NEUROTRANSMISORES

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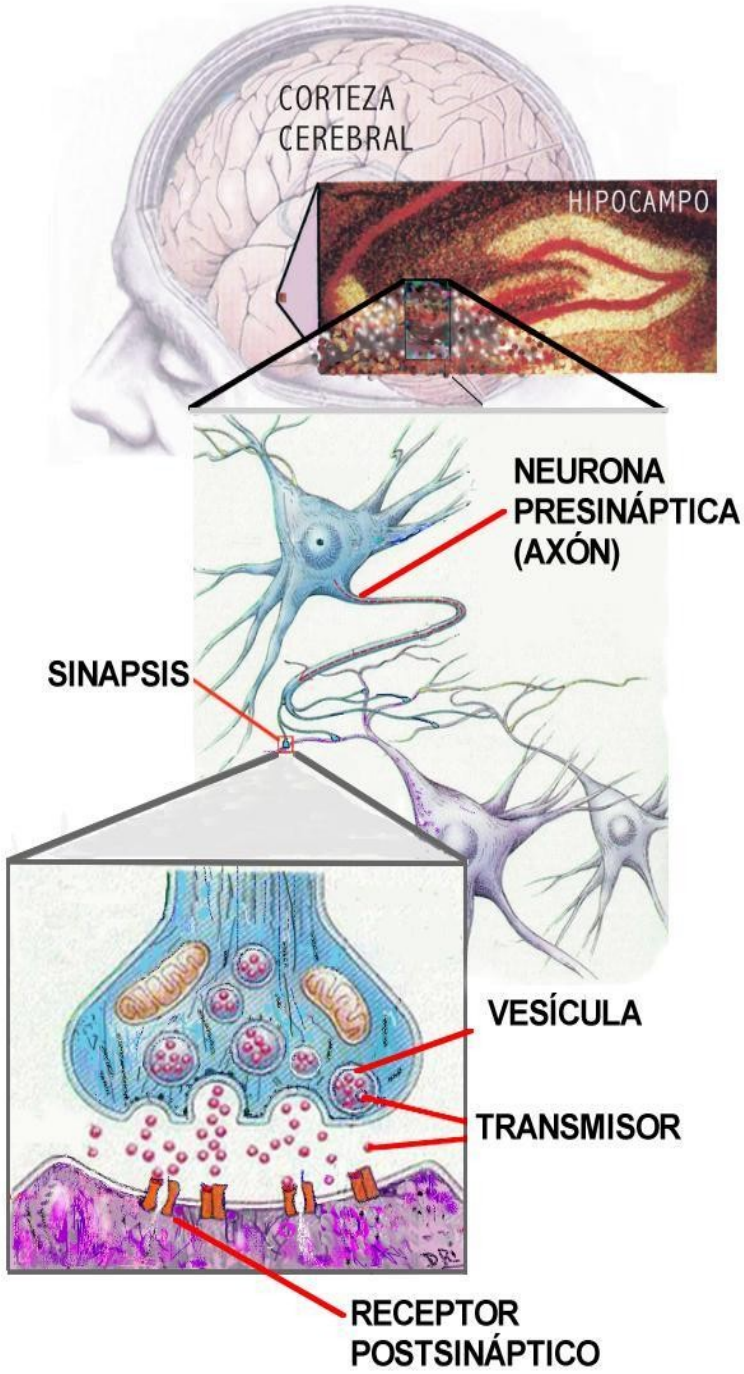
DOCENTE DE ANATOMIA

NEUROTRANSMISOR

- SUSTANCIAS QUIMICAS LIBERADAS A PARTIR DE VESICULAS PRESINAPTICAS, PRODUCEN UN CAMBIO EN EL POTENCIAL DE ACCION DE LA NEURONA POST SINAPTICA.


CORTEZA
CEREBRAL
HIPOCAMPO
NEURONA
PRESINÁPTICA
(AXÓN)
SINAPSIS
VESÍCULA
TRANSMISOR
RECEPTOR
POSTSINÁPTICO

Célula pre-sináptica
Célula post-sináptica
Tejido nervioso
Célula nerviosa

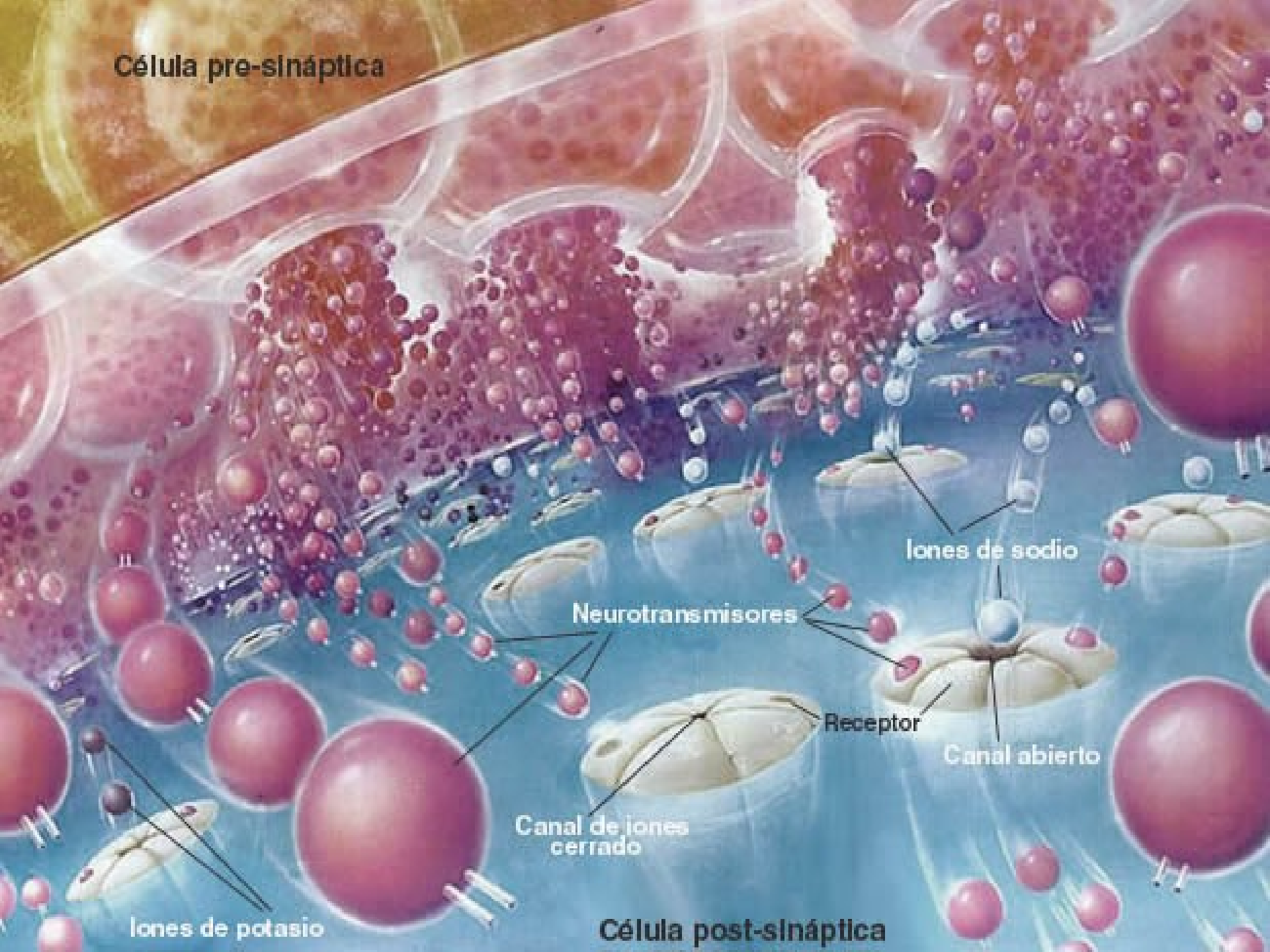
OTTO LOEWI

PRIMER NEUROTRANSMISOR

ACETILCOLINA

FUE AISLADO EN 1921 POR IN BIÓLOGO ALEMÁN OTTO LOEWI, QUIEN GANÓ PREMIO NOBEL 1936

FUNCIONES: ESTIMULACIÓN DE LOS MÚSCULOS, INCLUYENDO LOS MÚSCULOS DEL SISTEMA GASTRO-INTESTINAL. TAMBIÉN SE ENCUENTRA EN NEURONAS SENSORIALES Y EN EL SISTEMA NERVIOSO AUTÓNOMO, Y PARTICIPA EN LA PROGRAMACIÓN DEL SUEÑO REM.


Célula pre-sináptica
Iones de sodio
Neurotransmisores
Receptor
Canal abierto
Canal de iones cerrado
Iones de potasio
Célula post-sináptica

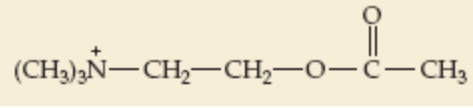
CLASIFICACION DE LOS AMINOACIDOS NEUROTRANSMISORES

- INHIBITORIOS: GABA, TAURINA, GLICINA Y ALANINA

ACTUAN SOBRE RE ASOCIADOS A CANALES IONICOS, ABREN CANALES DE CLORO E HIPERPOLARIZAN LA MEMBRANA POSTSINAPTICA Y DISMINUYE ACTIVIDAD NEURONAL.

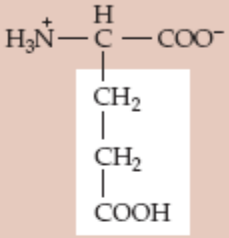
SMALL-MOLECULE NEUROTRANSMITTERS

Acetylcholine

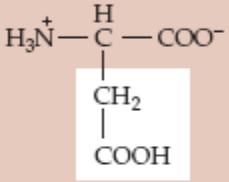


AMINO ACIDS

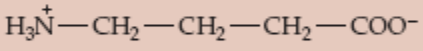
Glutamate



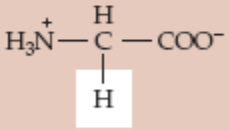
Aspartate

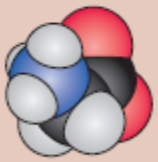


GABA



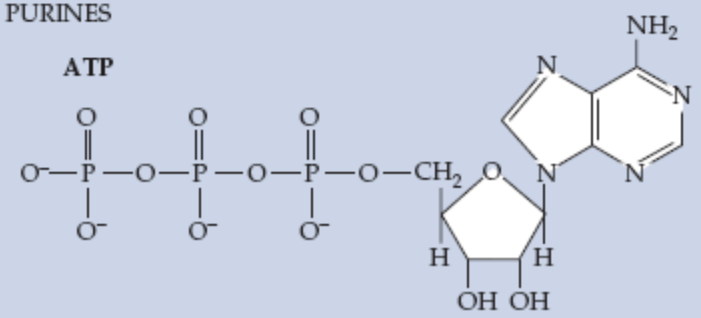
Glycine





PURINES

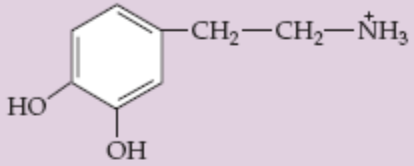
ATP



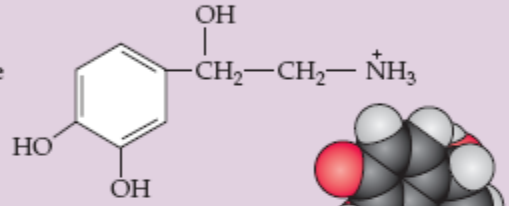
BIOGENIC AMINES

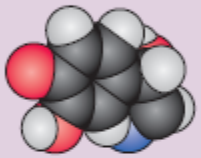
CATECHOLAMINES

Dopamine

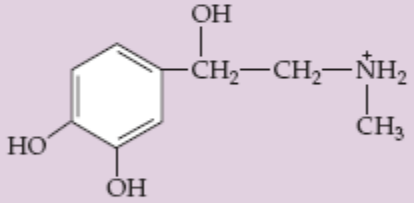


Norepinephrine



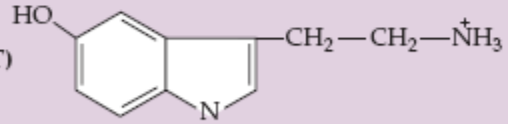


Epinephrine



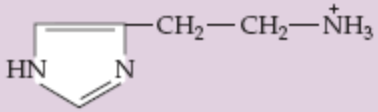
INDOLEAMINE

Serotonin (5-HT)



IMIDAZOLEAMINE

Histamine



CLASIFICACION DE LOS AMINOACIDOS NEUROTRANSMISORES

- EXCITATORIOS: HOMOCISTEICO, ASPARTAMICO Y GLUTAMICO

ACTUAN EN RE ASOCIADOS A CANALES IONICOS, ABREN LOS CANALES DE NA, DESPOLARIZAN LA MEMBRANA POSTSINAPTICA Y AUMENTAN LA ACTIVIDAD NEURONAL.

(A)

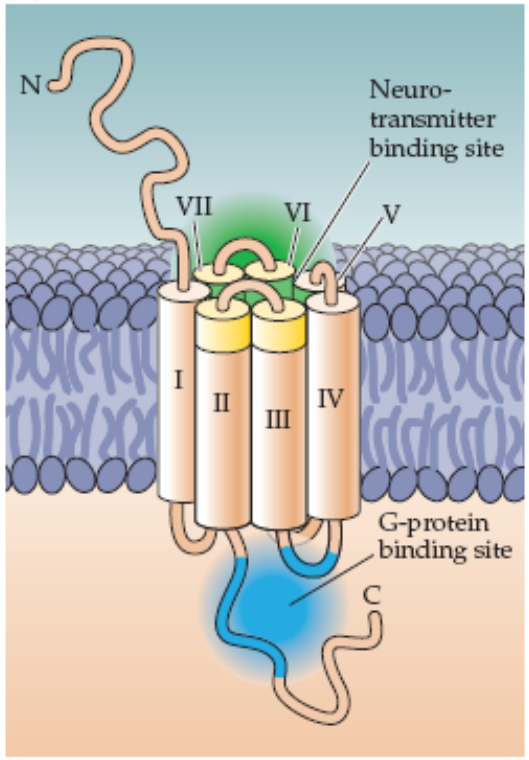
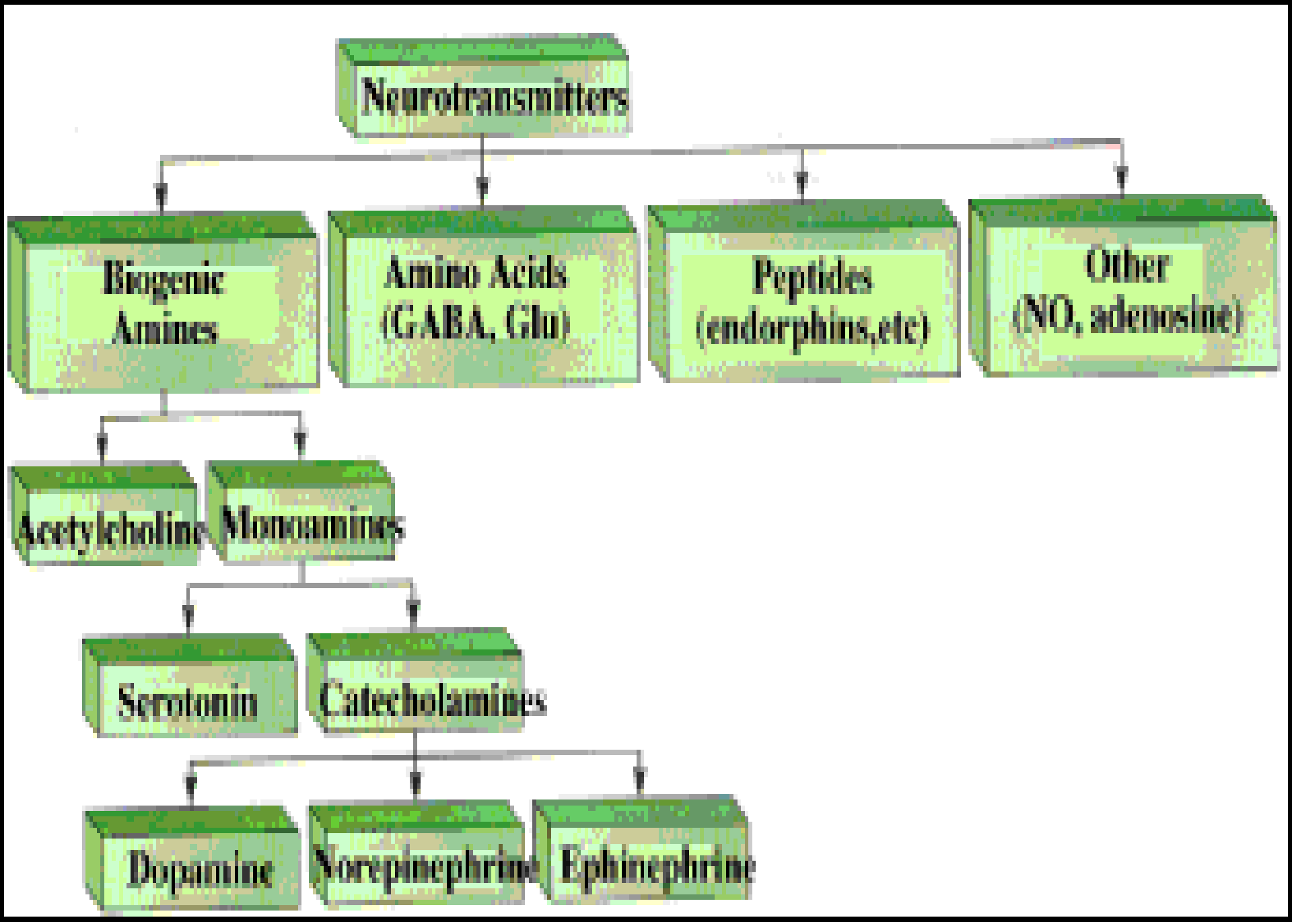


Figure 6.5 Structure and function of metabotropic receptors. (A) The transmembrane architecture of metabotropic receptors. These monomeric proteins contain seven transmembrane domains. Portions of domains II, III, VI, and VII make up the neurotransmitter-binding region. G-proteins bind to both the loop between domains V and VI and to portions of the C-terminal region. (B) Varieties of metabotropic neurotransmitter receptors.

(B)

Receptor class	Glutamate	$GABA_B$	Dopamine	NE, Epi	Histamine	Serotonin	Purines	Muscarinic
Receptor subtype	Class I	$GABA_B$ R1	$D1_A$	α1	H1	5-HT 1	A type	M1
	mGlu R1	$GABA_B$ R2	$D1_B$	α2	H2	5-HT 2	A1	M2
	mGlu R5		D2	β1	H3	5-HT 3	A2a	M3
	Class II		D3	β2		5-HT 4	A2b	M4
	mGlu R2		D4	β3		5-HT 5	A3	M5
	mGlu R3					5-HT 6	P type	
	Class III					5-HT 7	P2x	
	mGlu R4						P2y	
	mGlu R6						P2z	
	mGlu R7						P2t	
	mGlu R8						P2u	


Neurotransmitters
Biogenic Amines
Amino Acids (GABA, Glu)
Peptides (endorphins,etc)
Other (NO, adenosine)
Acetylcholine
Monoamines
Serotonin
Catecholamines
Dopamine
Norepinephrine
Ephinephrine

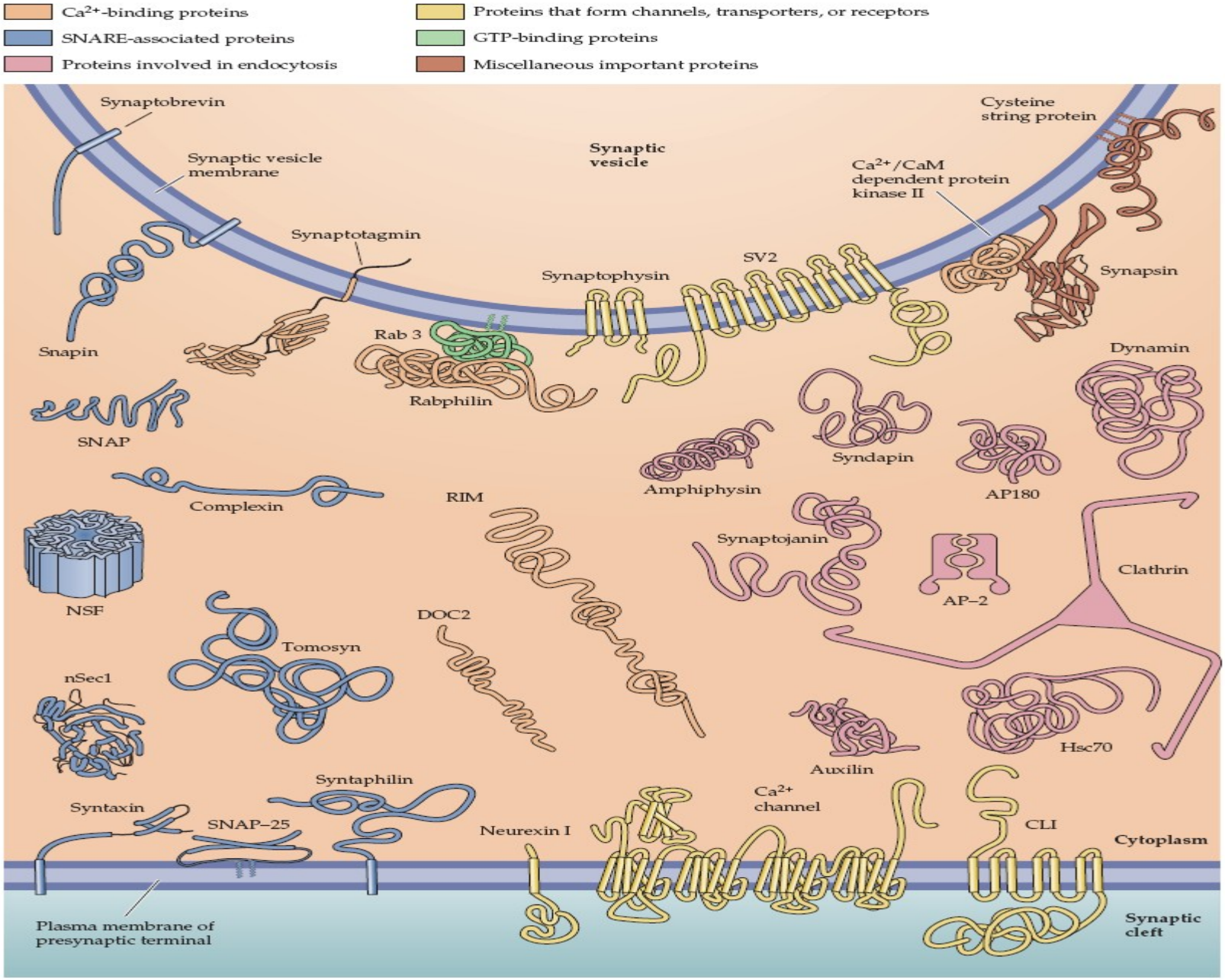


Figure 5.13 Presynaptic proteins implicated in neurotransmitter release. Structures adapted from Brunger (2001) and Brodsky et al. (2001).

NEUROMODULADORES

SUSTANCIAS PEPTIDICAS SE ORIGINAN FUERA DE LA SINAPSIS Y MODIFICAN LA EXCITABILIDAD NEURONAL

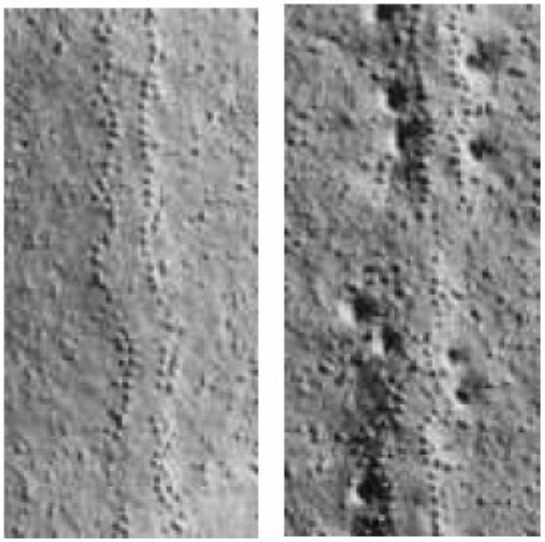
EJ: NEUROPEPTIDOS, SUSTANCIA P Y PROSTAGLANDINAS

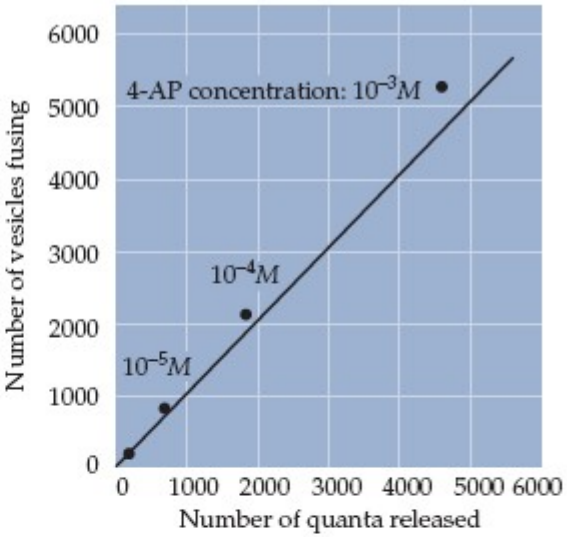
NO QUEDA RESTRINGIDO AL ESPACIO SINAPTICO DIFUNDE POR EL ESPACIO EXTRACELULAR.

EJ: ATP, ADENOSINA, GTP Y FENILETILAMINA

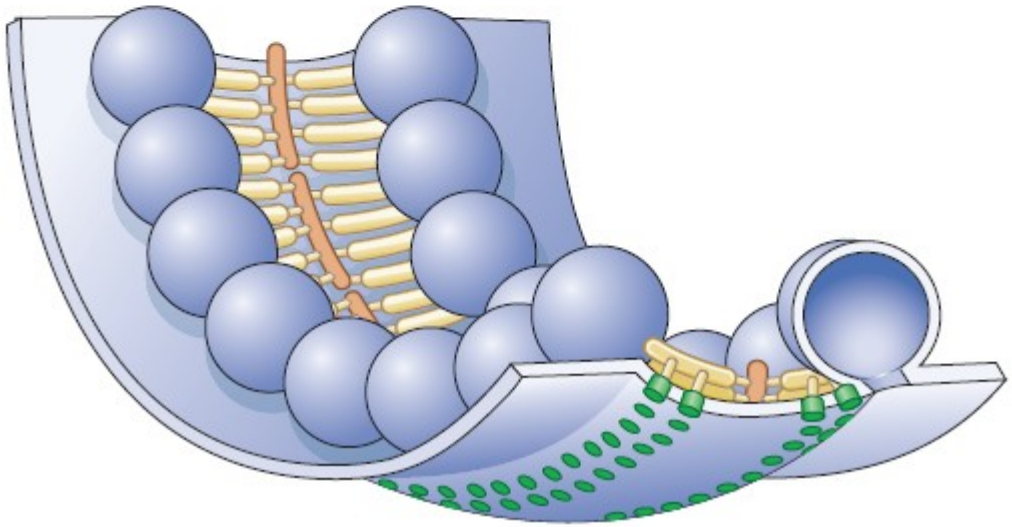
EVENTOS QUIMICOS ASOCIADOS A NEUROTRANSMISION

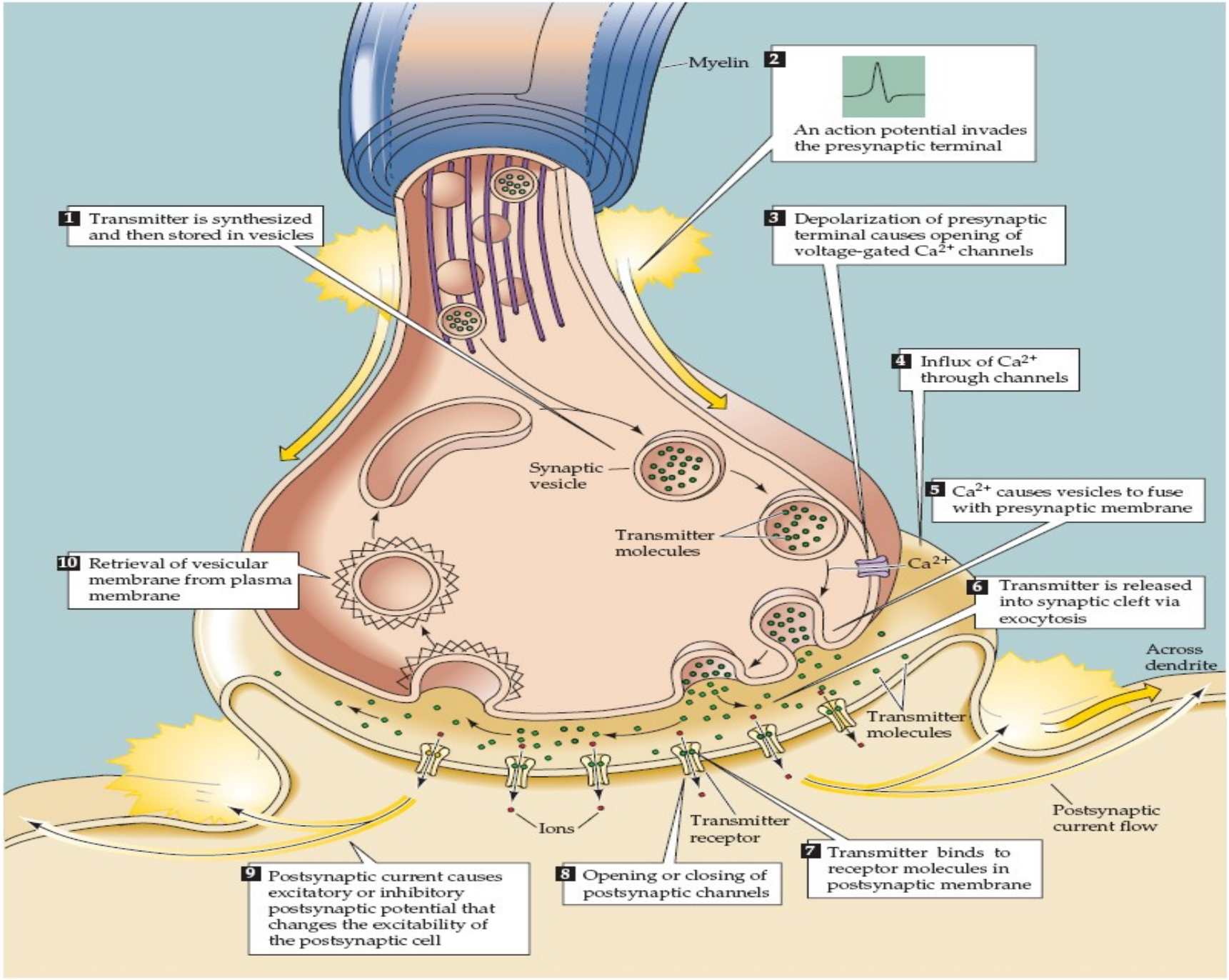
- SINTESIS
- ALMACENAMIENTO EN VESICULAS PRESINAPTICAS
- LIBERACION POR EXOCITOSIS CA +2 DEPENDIENTE
- UNIDO AL NEURO RE ACTIVA LA MEM. PLASMATICA DE LA NEURONA POSTSINAPTICA
- ACCION DEL 2DO MENSAJERO
- INACTIVACION DEL NEUROTRANSMISOR




6000
5000
4000
3000
2000
1000
0
Number of vesicles fusing
4-AP concentration: $10^{-3}M$
$10^{-4}M$
$10^{-5}M$
0
1000
2000
3000
4000
5000
6000
Number of quanta released

(C)




Myelin
2 An action potential invades the presynaptic terminal
1 Transmitter is synthesized and then stored in vesicles
3 Depolarization of presynaptic terminal causes opening of voltage-gated Ca^{2+} channels
4 Influx of Ca^{2+} through channels
Synaptic vesicle
5 Ca^{2+} causes vesicles to fuse with presynaptic membrane
Transmitter molecules
Ca^{2+}
10 Retrieval of vesicular membrane from plasma membrane
6 Transmitter is released into synaptic cleft via exocytosis
Across dendrite
Transmitter molecules
Ions
Transmitter receptor
Postsynaptic current flow
9 Postsynaptic current causes excitatory or inhibitory postsynaptic potential that changes the excitability of the postsynaptic cell
8 Opening or closing of postsynaptic channels
7 Transmitter binds to receptor molecules in postsynaptic membrane

NEUROTRANSMISORES: ADRENERGICOS

- DEPRESORES: ADRENALINA, DOPAMINA Y SEROTONINA
- ESTIMULANTES: FENIL ETILAMINA (NORADRENALINA, DOPAMINA Y TIRAMINA)
- RE ADRENERGICOS:

  ALFA 1: NA Y AD

  ALFA 2: AD Y NA

  BETA 1: AD, NA Y DA

  BETA 2: AD.
- NUCLEOS DE ALMACENAMIENTO: LOCUS CERULEUS Y SUBCERULEO.
- FACILITA: ATENCION Y APRENDIZAJE

NEUROTRANSMISOR: DOPAMINERGICO

- RESERVORIO EN LOCUS NIGER
- RE:

D1 ALTA AFINIDAD AGONISTA: PROT DE ACOPLE ENTRE RE Y ADENILATOCICLASA, INCREMENTANDO SINTESIS DE AMPC.

D2 BAJA AFINIDAD INH. ADENILCICLASA Y DISMINUYEN SINTESIS DE AMPC.

CONTROL MOTOR VOLUNTARIO Y FUNCIONES COGNITIVAS

DEFICIT = PARKINSON,

AUMENTO = ESQUIZOFRENIA

NEUROTRANSMISOR: DERIVADOS DEL TRIPTOFANO

- **SEROTONINA** DEPENDE DE S HIPOTALAMO HIPOFISIS. N DORSAL DEL RAFE Y RAFE MEDIANO.

BIOSINTESIS DISMINUYE: ADRENALECTOMIA Y AUMENTA CON GLUCOCORTICOIDES.

FAVORECE CONSOLIDACION Y RECUPERACION DE MEMORIA

AUMENTA CON ANSIEDAD, FOBIAS Y PANICO

- BUFOTENINA O N DMETIL SEROTONINA IV= ALT SIMILARES A ESQUIZOFRENIA

NEUROTRANSMISOR: ACETIL COLINA

- SINTESIS A PARTIR DE COLINA ACETILTRANSFERASA Y SE INACTIVA POR LA ACETIL COLINESTERASA EN COLINA Y ACETATO.
- ALMACENADA DE FORMA ESTABLE EN LAS VESICULAS
- AL DESPOLARIZARSE LA MEMB, ENTRA CA Y NA Y SALE LA ACo A LA HENDIDURA SINAPTICA
- RE: NICOTINICOS DE RESPUESTA RAPIDA Y MUSCARINICOS PRE Y POSTSINAPTICOS

NEUROTRANSMISOR: SISTEMA AMINOACIDÈRGICO

- INHIBITORIO GABA Y GLICINA

GABA NEOCORTEZA Y ESTRIO PALIDAL

RE GABA A ABREN CANALES DE CLORO

RE GABA B ABREN CA CALCIO

MANIFESTACIONES: ANTICONVULSIVANTES Y ANTIAGRESIVAS

AUMENTA LIBERACION DE PRL Y GH

- EXCITATORIO GLUTAMATO Y ASPARTATO

NEUROTRANSMISOR: HISTAMINA

- SE FORMA POR DECARBOXILACIÓN DEL AMINOÁCIDO HISTIDINA CATALIZADA POR LA HISTIDINA DECARBOXILASA
- LA HISTAMINA SE ENCUENTRA EN VESÍCULAS SINÁPTICAS Y SE LIBERA POR CONCENTRACIONES DESPOLARIZANTES DE K+.
- DOS TIPOS DE RE HISTAMINÉRGICOS, LOS H1 Y LOS H2
- LAS NEURONAS HISTAMINÉRGICAS CONTROLAN EL ESTADO DE VIGILANCIA. COLIBERA CON LA SUSTANCIA P Y LA SOMATOSTATINA FAVORECIENDO A TRAVÉS DE LA PRIMERA LA TRASMISIÓN DEL DOLOR Y DE LA SEGUNDA LA ESTIMULACIÓN DE LOS LINFOCITOS T QUE PARTICIPAN DEL FENÓMENO INMUNITARIO.

CARACTERISTICAS DE LOS AMINOACIDOS

- ASPARTAMICO Y GLUTAMICO SON AMINOACIDOS NO ESENCIALES, NO ATRAVIESAN LA BARRERA HEMATOENCEFALICA
- SINTETIZADOS A PARTIR DE GLUCOSA Y PRECURSORES GLUTAMINA

NEUROTRANSMISOR: FENIL ETIL AMINA (FEA)

NEOCORTICAL PREDOMINA DURANTE LA VIGILIA, ACTUANDO COMO UNA ANFETAMINA BIOLÓGICA, DEPENDIENDO DE ELLA EL ÍNDICE DE VIGILANCIA.

NEUROPÉPTIDOS

PÉPTIDOS COMPLEJOS QUE ACTÚAN COMO COMENSAJEROS, COLIBERANDO CON EL NEUROTRANSMISOR Y MODULANDO SU ACCIÓN.

SE CLASIFICAN EN OPIOIDES Y NO OPIOIDES.

ACTÚAN COMO NEUROHORMONAS,

Y COMO MODULADORES DE NEUROTRANSMISORES.

SE SINTETIZAN EN EL RETÍCULO ENDOPLÁSMICO RUGOSO COMO UNA MOLÉCULA PRECURSORA Y LUEGO EN EL COMPLEJO DE GOLGI EN FORMA MOLECULAR DE ENCEFALINAS, ENDORFINAS.

OPIOIDES

DERIVADOS MORFINA, LAS ENCEFALINAS, LAS ENDORFINAS Y LAS DINORFINAS.

ENCEFALINAS: RECEPTORES DELTA METENCEFALINA LEUENCEFALINA, ESTIMULANDO LA SECRECIÓN NEUROHIPOFISARIA, SIENDO INDISPENSABLES PARA LA MEMORIA Y MODULADORAS DE LA ACTIVIDAD AFECTIVA INSTINTUAL.

ESCOTOFOBINA PROVOCA MIEDO A LA OSCURIDAD.

ENDORFINAS: BETA ENDORFINAS ACTÚAN DE PREFERENCIA SOBRE LOS RECEPTORES MU, INHIBIENDO LA SECRECIÓN ADENOHIPOFISARIA DE LH, SIENDO CONSIDERADAS UNA PROVOCANDO ANALGESIA Y SOMNOLENCIA.

DINORFINAS ACTÚAN DE PREFERENCIA SOBRE LOS RECEPTORES KAPPA NEUROHIPOFISARIOS..

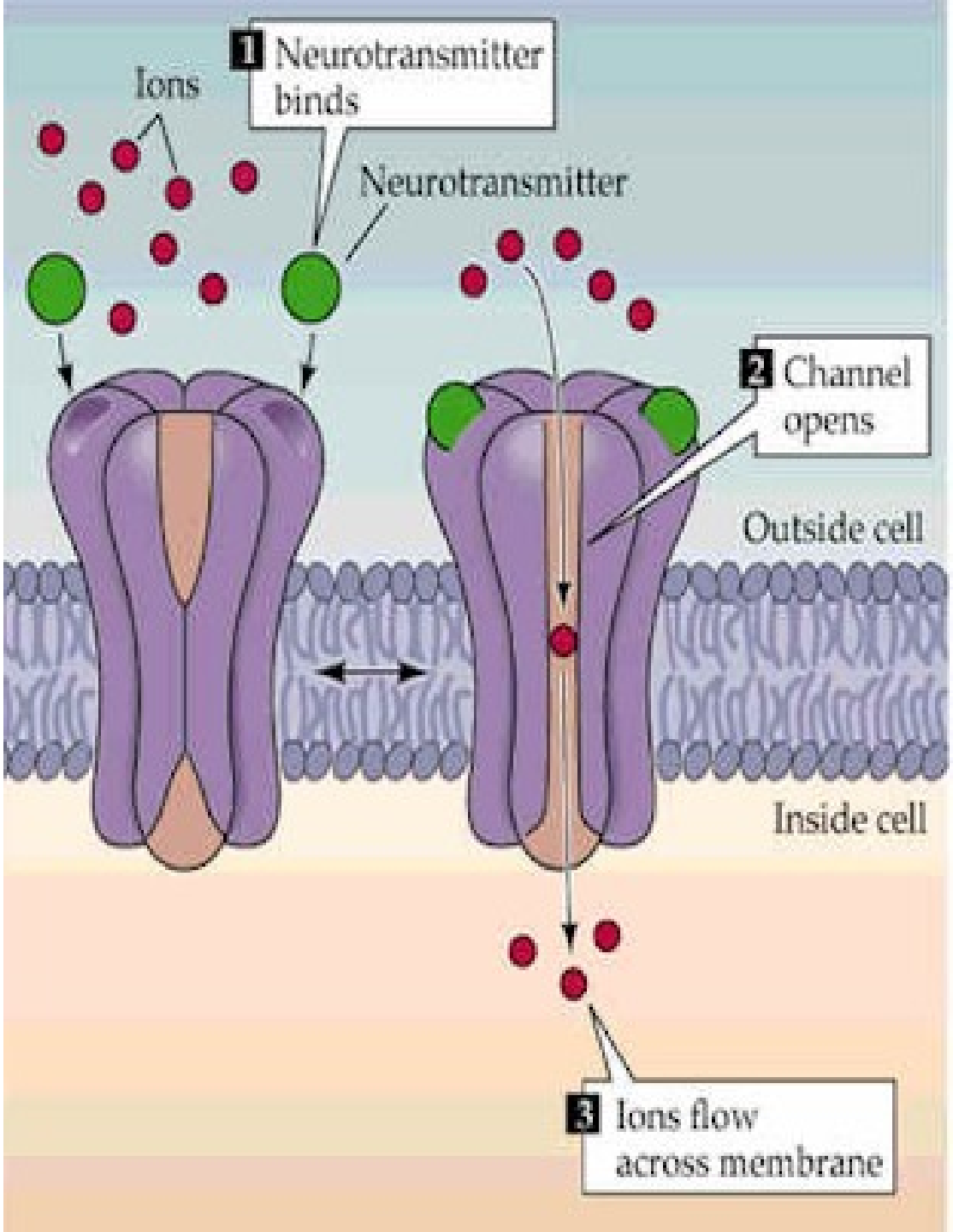
LOS RECEPTORES PUEDEN SER:

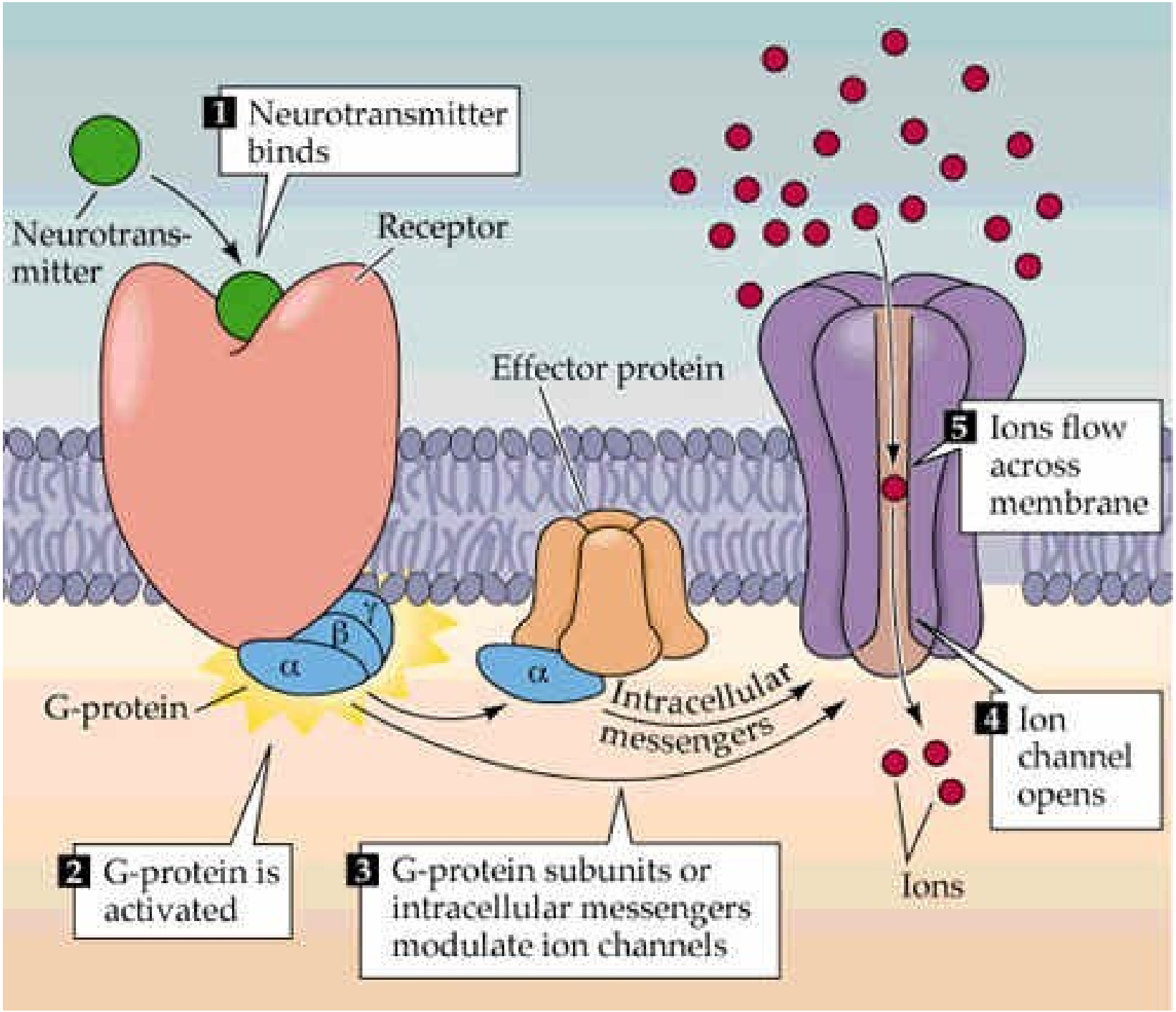
- RECEPTORES SENSORIALES

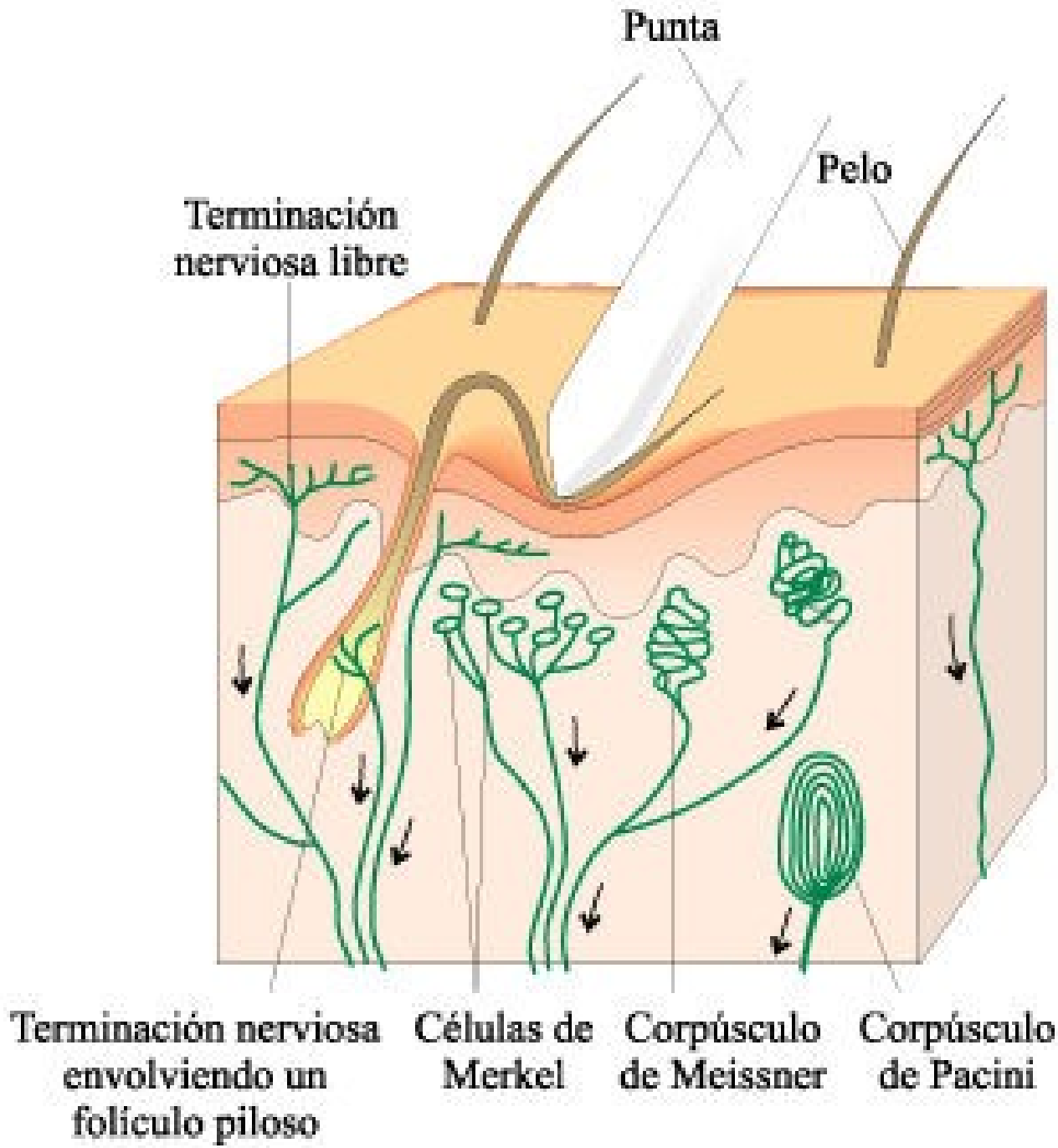
MECANORECEPTORES, TERMORECEPTORES, FOTORECEPTORES, NOCICEPTORES,

QUIMIORECEPTORES

- RECEPTORES IONOTRÓFICOS
- RECEPTORES METABOTRÓFICOS


Ions
1 Neurotransmitter binds
Neurotransmitter
2 Channel opens
Outside cell
Inside cell
3 Ions flow across membrane


1 Neurotransmitter binds
Neurotrans-mitter
Receptor
Effector protein
5 Ions flow across membrane
β
γ
α
α
G-protein
Intracellular messengers
4 Ion channel opens
Ions
2 G-protein is activated
3 G-protein subunits or intracellular messengers modulate ion channels

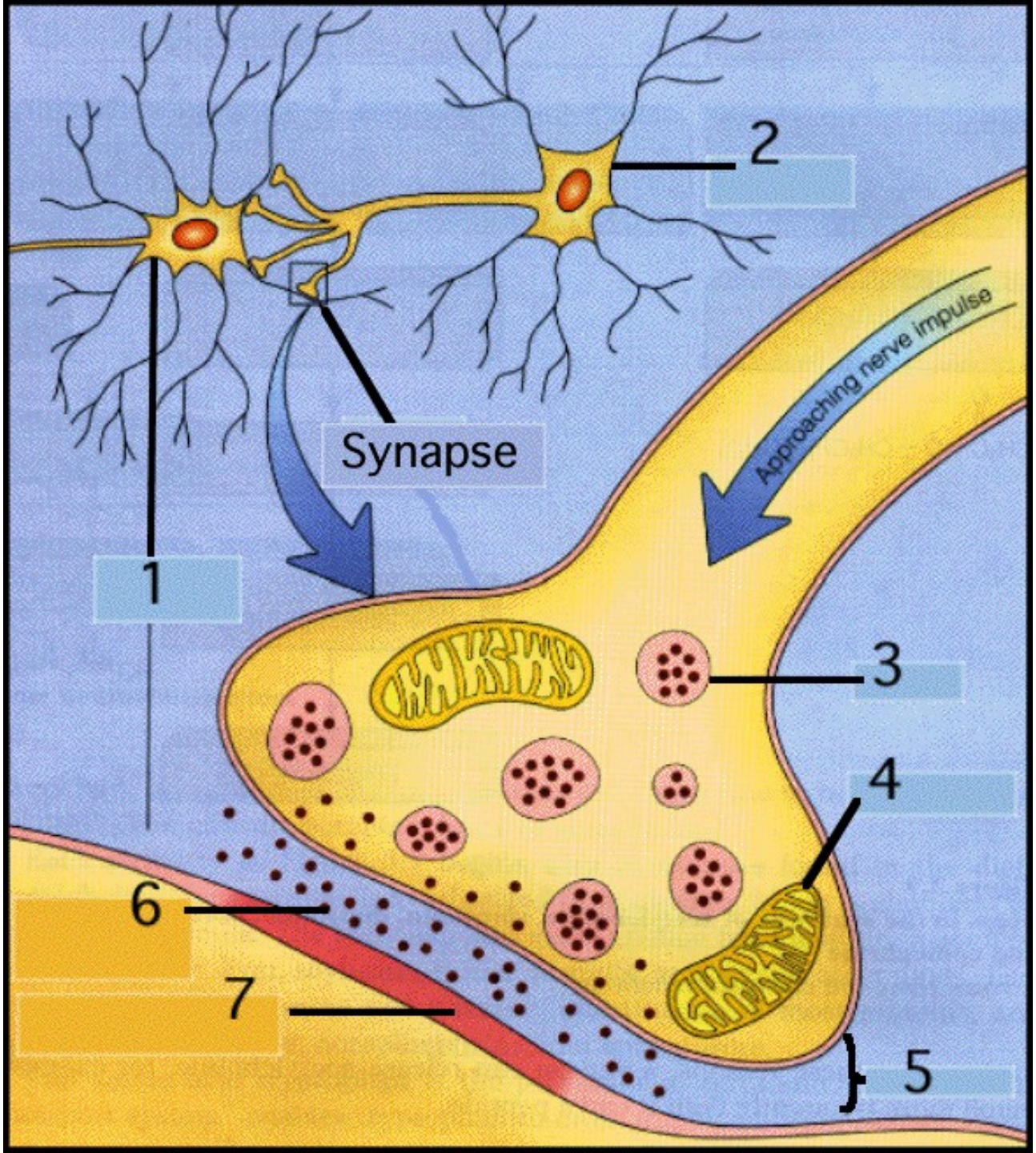

Punta
Pelo
Terminación nerviosa libre
Terminación nerviosa envolviendo un folículo piloso
Células de Merkel
Corpúsculo de Meissner
Corpúsculo de Pacini

SINAPSIS QUIMICA

EL NEUROTRANSMISOR HACE DE PUENTE ENTRE LAS DOS NEURONAS, SE DIFUNDE A TRAVÉS DEL ESTRECHO ESPACIO Y SE ADHIERE A LOS RECEPTORES.

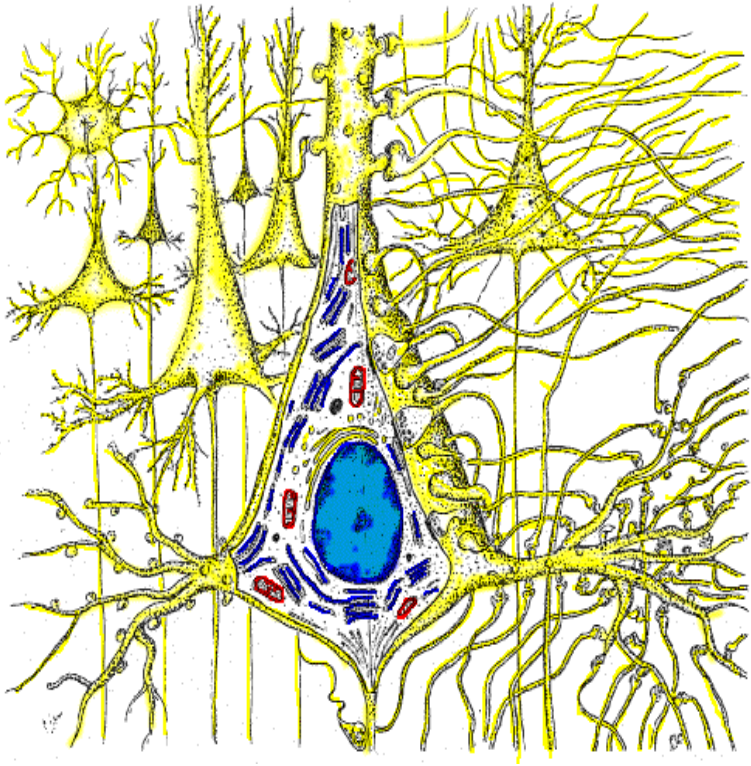
LA ENERGÍA REQUERIDA PARA LA LIBERACIÓN DE UN NEUROTRANSMISOR SE GENERA EN LA MITOCONDRIA DEL TERMINAL PRESINÁPTICO.

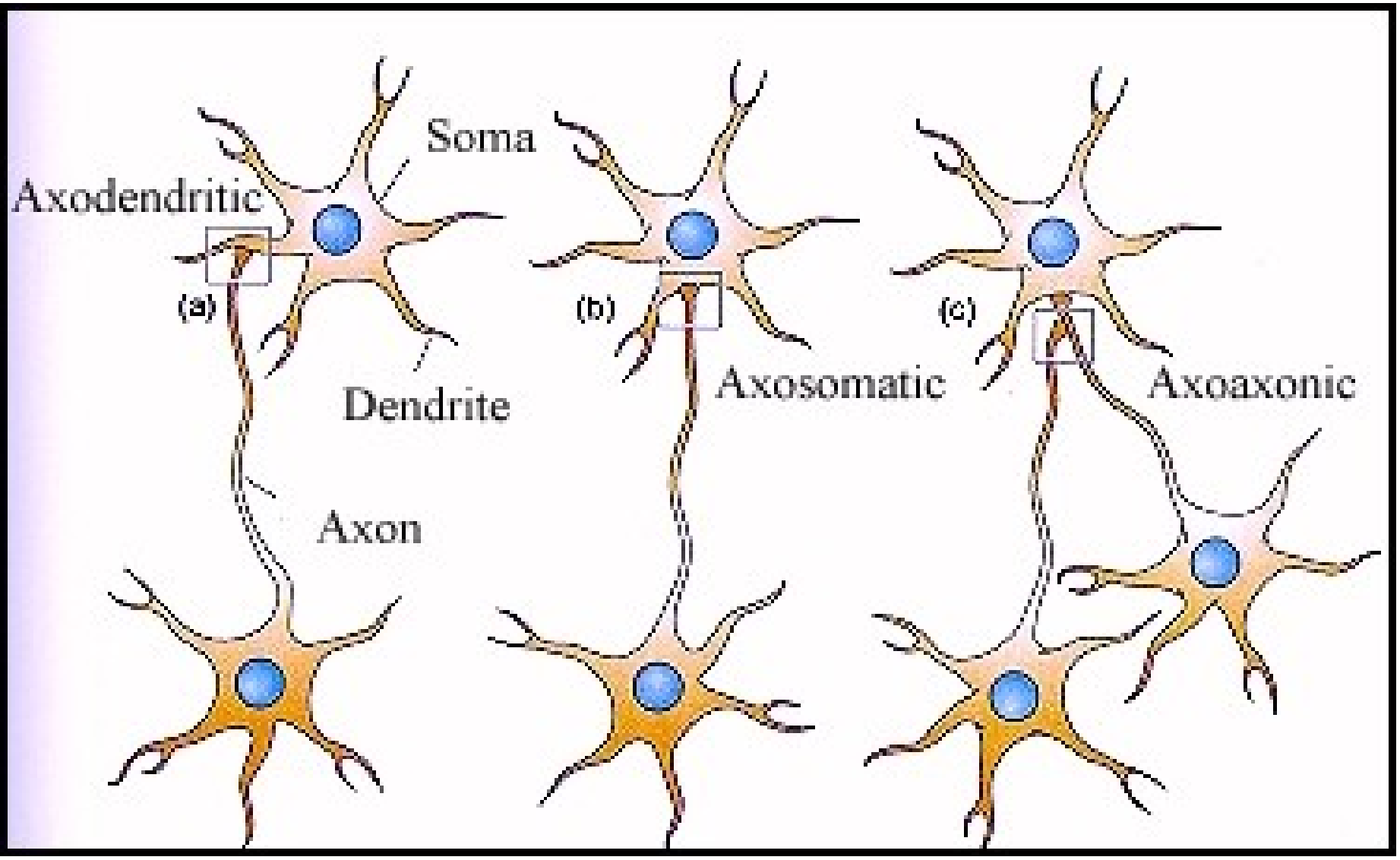
LA UNIÓN DE NEUROTRANSMISORES A RECEPTORES DE LA MEMBRANA POSTSINÁPTICAS PRODUCE CAMBIOS EN LA PERMEABILIDAD DE LA MEMBRANA.


2
Synapse
Approaching nerve impulse
1
3
4
6
7
5

VARIAS FORMAS DE SINAPSIS SEGÚN LAS ESTRUCTURAS IMPLICADAS

AXOSOMÁTICA
AXODENDRÍTICA
AXOESPINODENDRÍTICA
AXOAXÓNICA
DENDRODENDRÍTICA
SOMATOSOMÁTICA
DENDROSOMÁTICA




Soma
Axodendritic
(a)
Dendrite
Axon
(b)
Axosomatic
(c)
Axoaxonic

ETAPAS DE LA SINAPSIS

- PRIMERA ETAPA: REGULACIÓN DE LA SÍNTESIS DEL NEUROTRANSMISOR
- SEGUNDA ETAPA: LIBERACIÓN DEL NEUROTRANSMISOR
- TERCERA ETAPA: ACTIVACIÓN DE RECEPTORES
- CUARTA ETAPA: INACTIVACIÓN DEL NEUROTRANSMISOR
- QUINTA ETAPA: DIFUSIÓN DEL NEUROTRANSMISOR

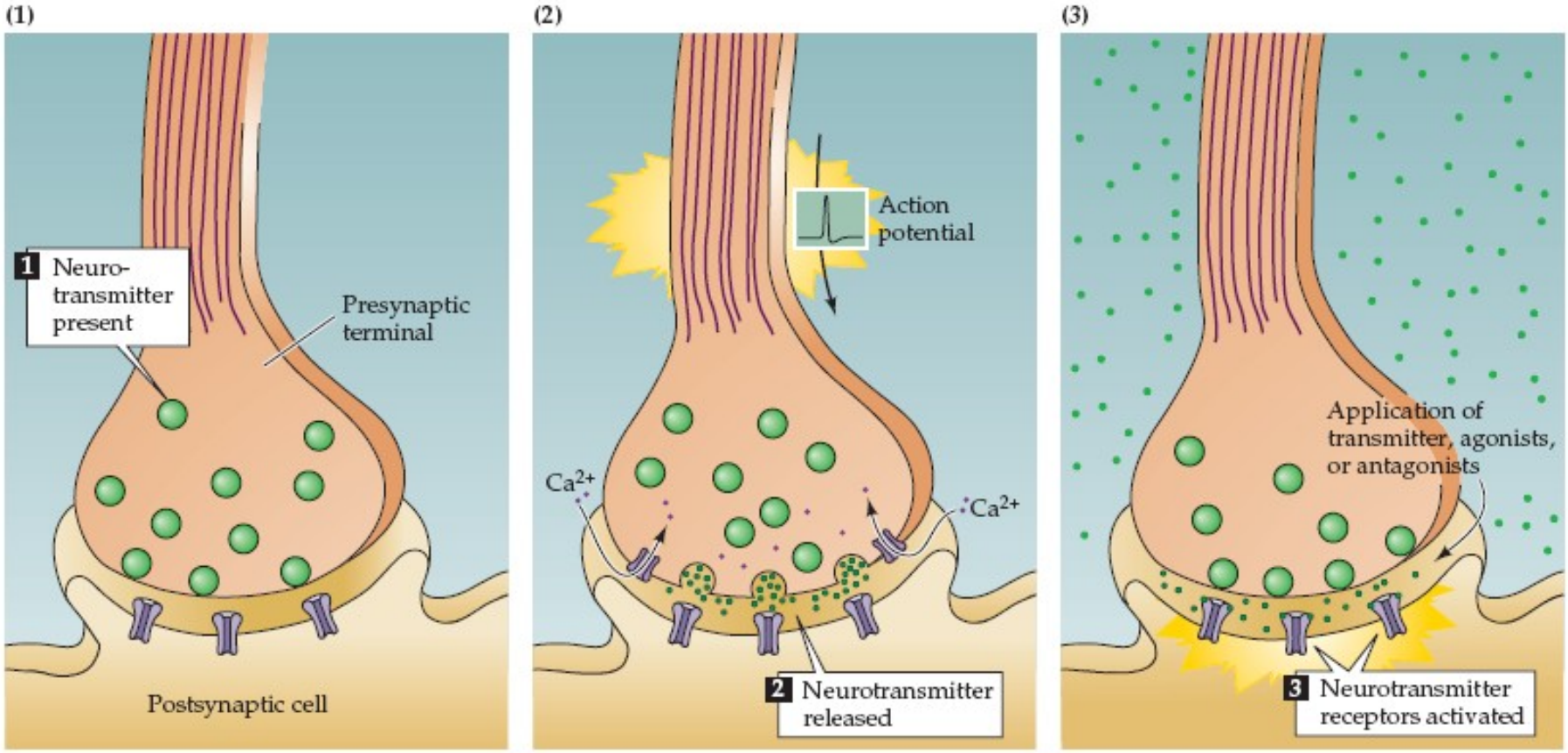
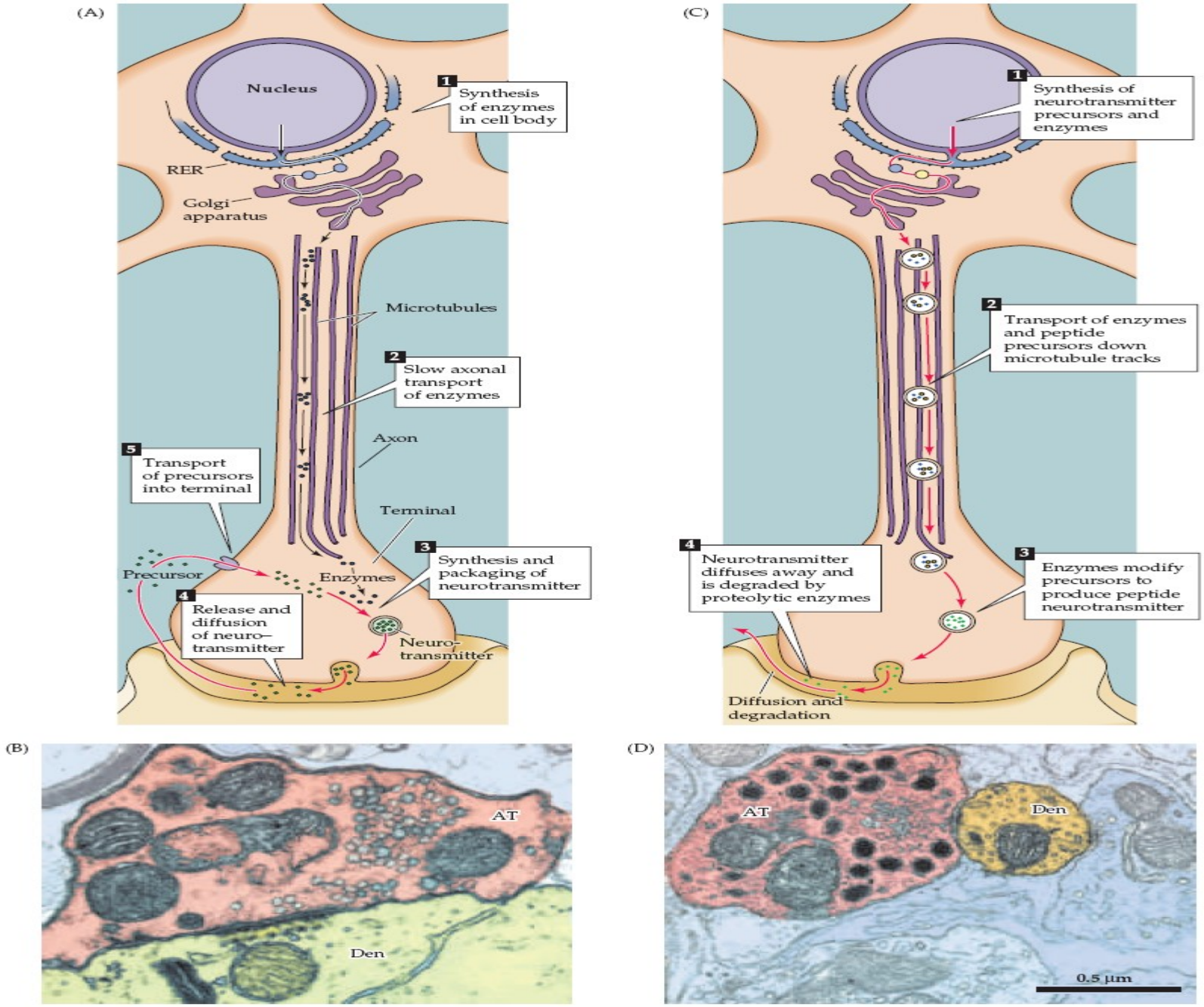
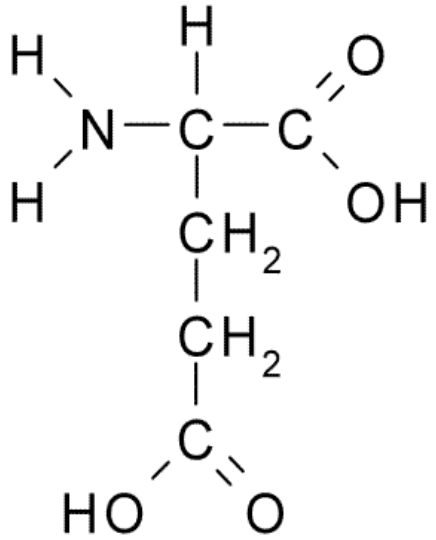


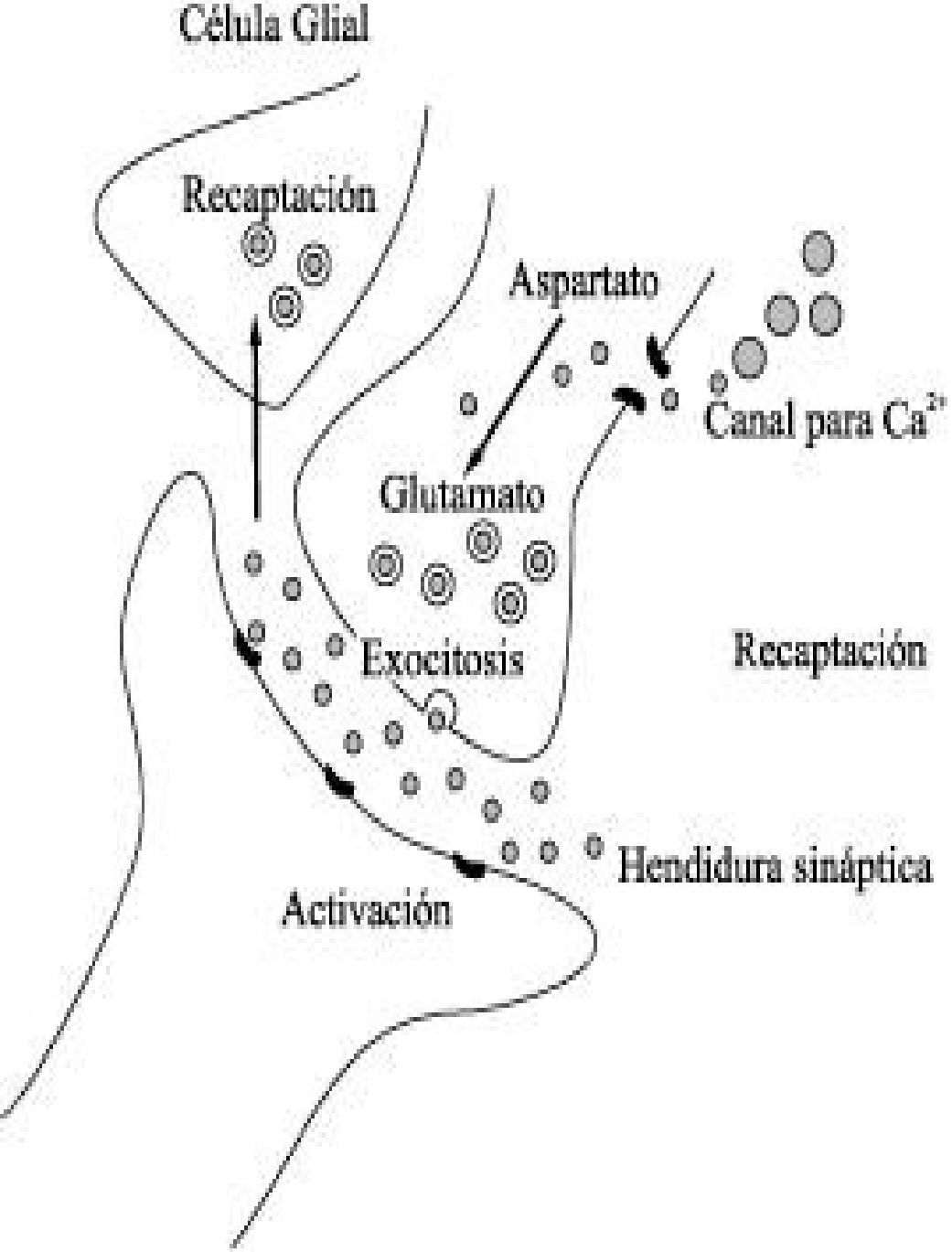
Figure 5.5 Metabolism of small-molecule and peptide transmitters. (A) Small-molecule neurotransmitters are synthesized at nerve terminals. The enzymes necessary for neurotransmitter synthesis are made in the cell body of the presynaptic cell (1) and are transported down the axon by slow axonal transport (2). Precursors are taken up into the terminals by specific transporters, and neurotransmitter synthesis and packaging take place within the nerve endings (3). After vesicle fusion and release (4), the neurotransmitter may be enzymatically degraded. The reuptake of the neurotransmitter (or its metabolites) starts another cycle of synthesis, packaging, release, and removal (5). (B) Small clear-core vesicles at a synapse between an axon terminal (AT) and a dendritic spine (Den) in the central nervous system. Such vesicles typically contain small-molecule neurotransmitters. (C) Peptide neurotransmitters, as well as the enzymes that modify their precursors, are synthesized in the cell body (1). Enzymes and propeptides are packaged into vesicles in the Golgi apparatus. During fast axonal transport of these vesicles to the nerve terminals (2), the enzymes modify the propeptides to produce one or more neurotransmitter peptides (3). After vesicle fusion and exocytosis, the peptides diffuse away and are degraded by proteolytic enzymes (4). (D) Large dense-core vesicles in a central axon terminal (AT) synapsing onto a dendrite (Den). Such vesicles typically contain neuropeptides or, in some cases, biogenic amines. (B and D from Peters, Palay, and Webster, 1991.)

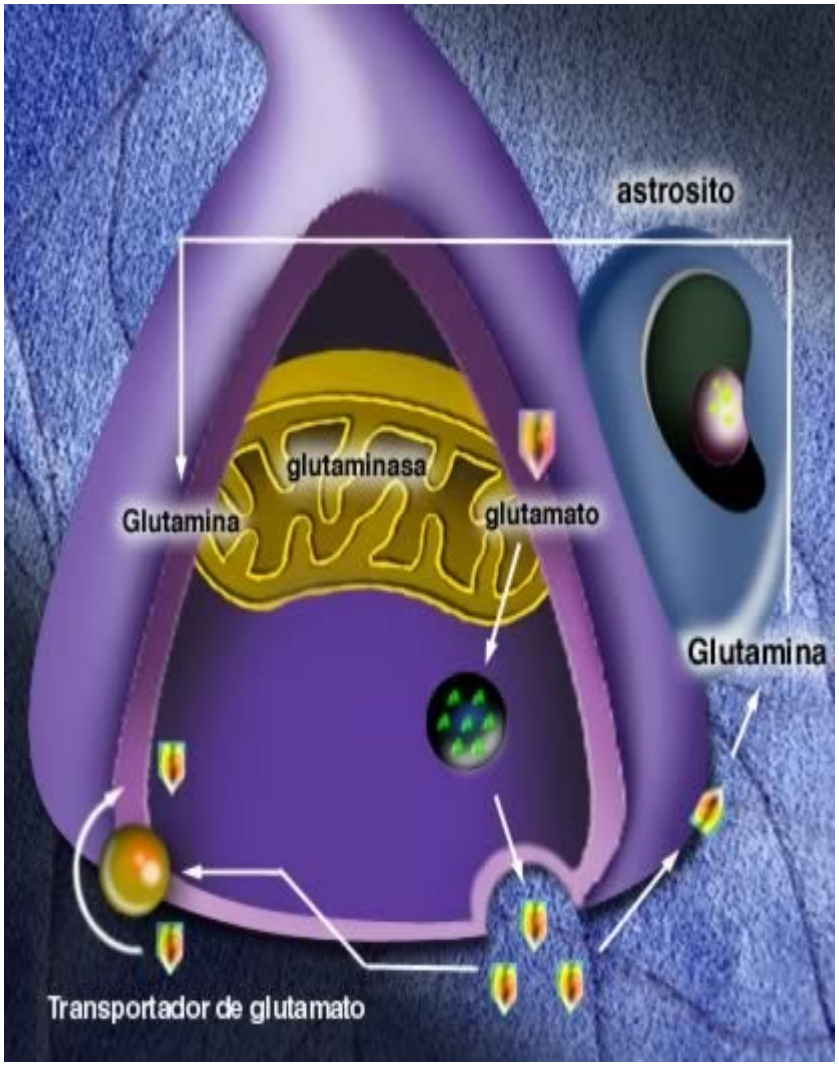

(A)
Nucleus
1 Synthesis of enzymes in cell body
RER
Golgi apparatus
Microtubules
2 Slow axonal transport of enzymes
Axon
5 Transport of precursors into terminal
Terminal
3 Synthesis and packaging of neurotransmitter
Precursor
Enzymes
4 Release and diffusion of neuro–transmitter
Neuro–transmitter
(C)
1 Synthesis of neurotransmitter precursors and enzymes
2 Transport of enzymes and peptide precursors down microtubule tracks
4 Neurotransmitter diffuses away and is degraded by proteolytic enzymes
3 Enzymes modify precursors to produce peptide neurotransmitter
Diffusion and degradation
(B)
AT
Den
(D)
AT
Den
0.5 µm

L- GLUTAMATO



- AMINOACIDO NO ESENCIAL
- 1950-1960 EXCITATORIO
- EL MAS COMÙN,
- PRINCIPALES VIAS: CORTEZA CEREBRAL, HIPOCAMPO, CEREBELO, ESTRIADO Y MEDULA ESPINAL.
- FUNCIONES COGNITIVAS ALTAS
- 80% FUNCION METABOLICA: SINTESIS PROTEICA Y DETOXIFICACION DEL AMONIACO.
- 20% NEUROTRANSMISOR


Célula Glial
Recaptación
Aspartato
Canal para Ca^{2+}
Glutamato
Exocitosis
Recaptación
Hendidura sináptica
Activación


astrosito
glutaminasa
Glutamina
glutamato
Glutamina
Transportador de glutamato

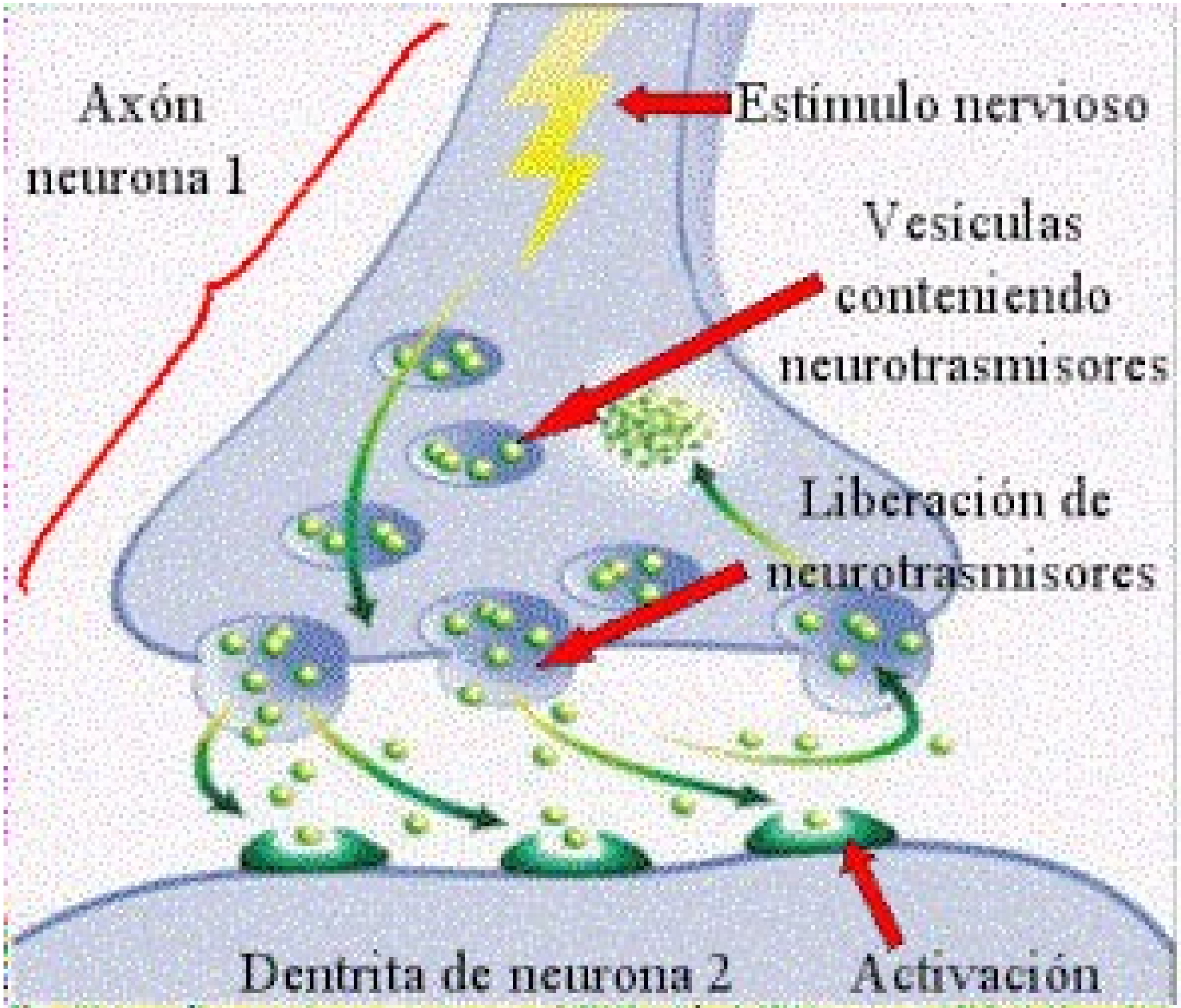
L- GLUTAMATO

CONCENTRACIÓN EN REPOSO:

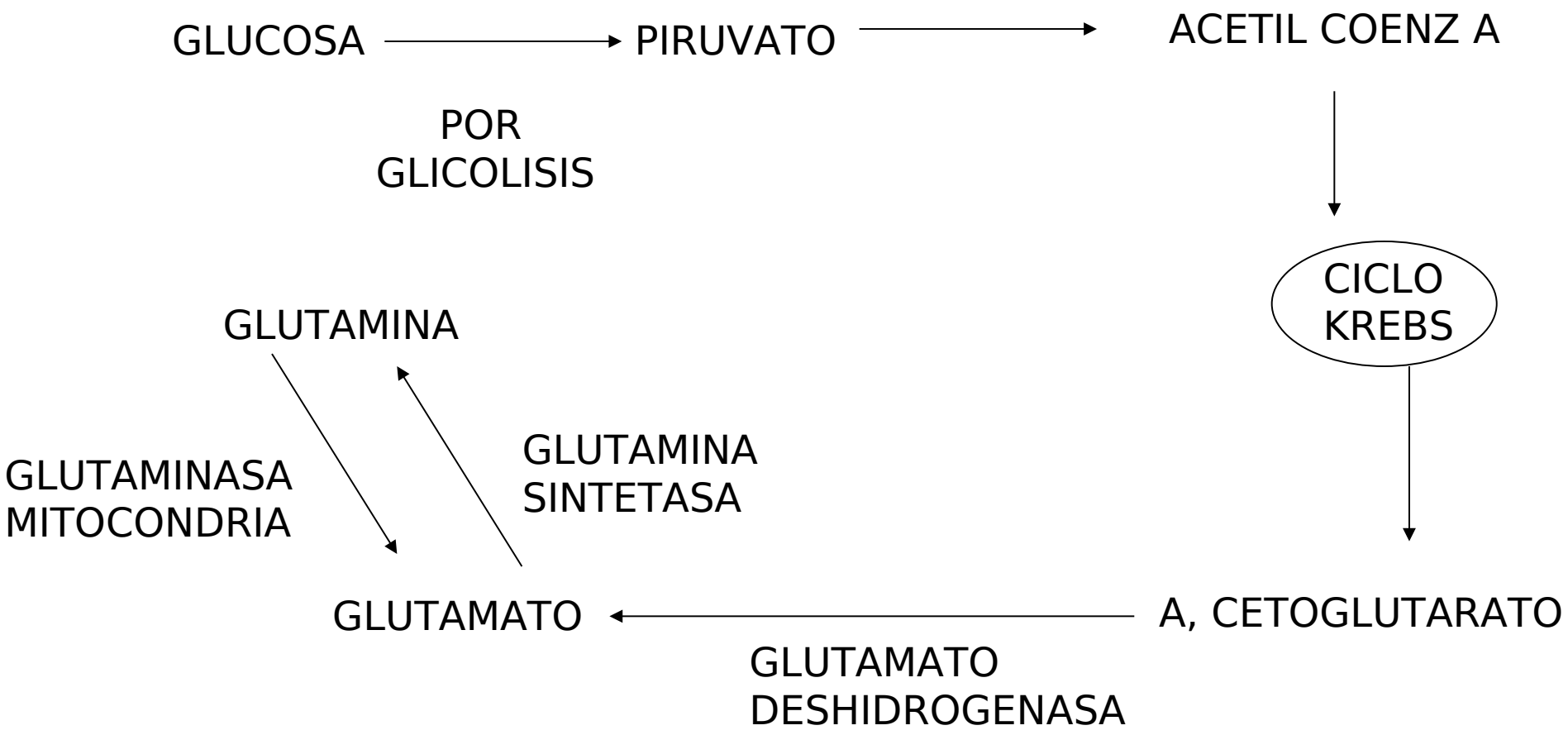
ESPACIO EXTRACELULAR ES DE 1 MICROMOL,

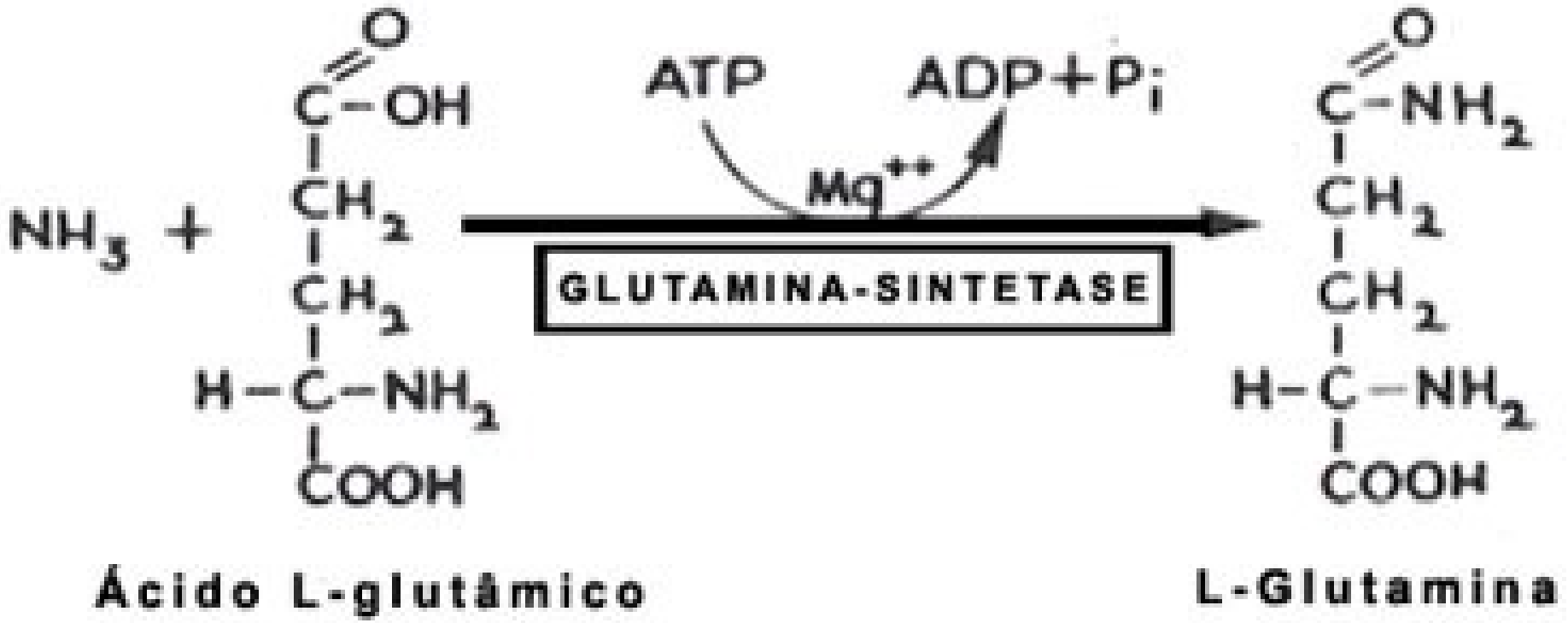
EN EL CITOPLASMA PRESINÁPTICO ES DE 10 MILIMOLES Y

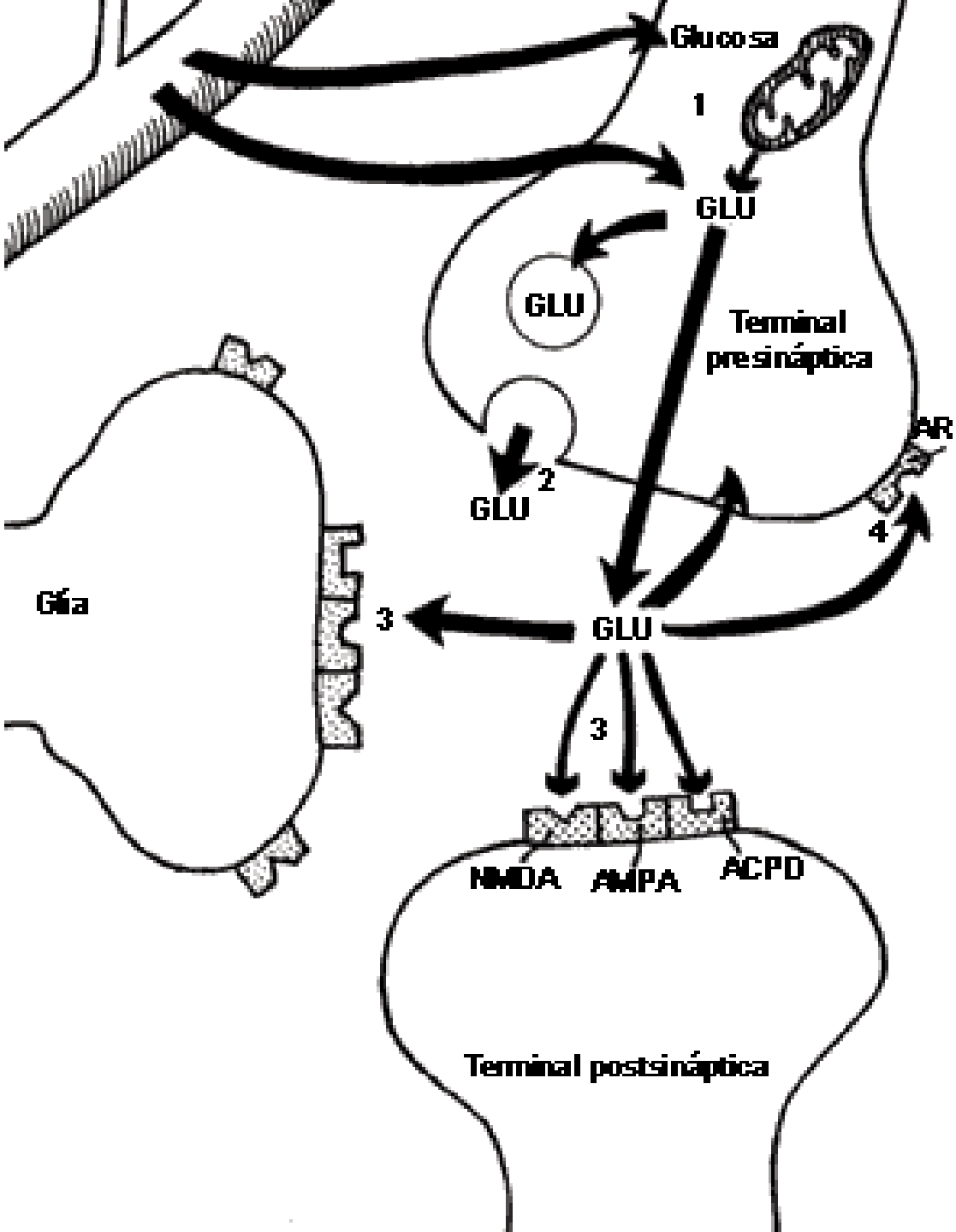
EN LAS VESÍCULAS DE ALMACENAMIENTO ES DE 100 MILIMOLES.


Axón
neurona 1
Estímulo nervioso
Vesículas
conteniendo
neurotrasmisores
Liberación de
neurotrasmisores
Dentrita de neurona 2
Activación

SINTESIS


GLUCOSA
PIRUVATO
ACETIL COENZ A
POR
GLICOLISIS
CICLO
KREBS
GLUTAMINA
GLUTAMINASA
MITOCONDRIA
GLUTAMINA
SINTETASA
GLUTAMATO
A, CETOGLUTARATO
GLUTAMATO
DESHIDROGENASA


ATP
ADP + Pi
Mg++
GLUTAMINA-SINTETASE
NH3 +
Ácido L-glutâmico
L-Glutamina


Glucosa
1
GLU
GLU
Terminal
presináptica
AR
2
GLU
4
Glía
3
GLU
3
NMDA
AMPA
ACPD
Terminal postsináptica

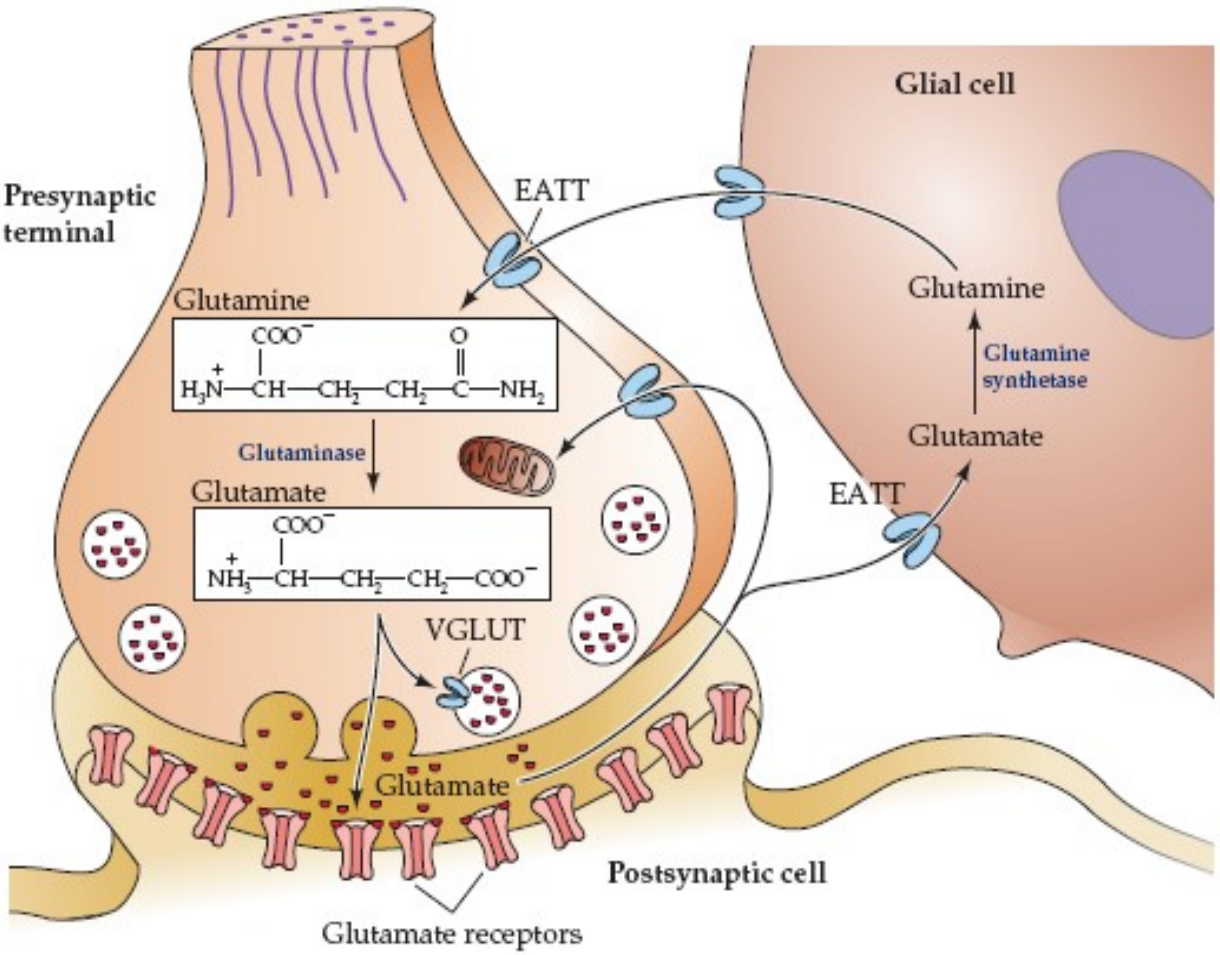
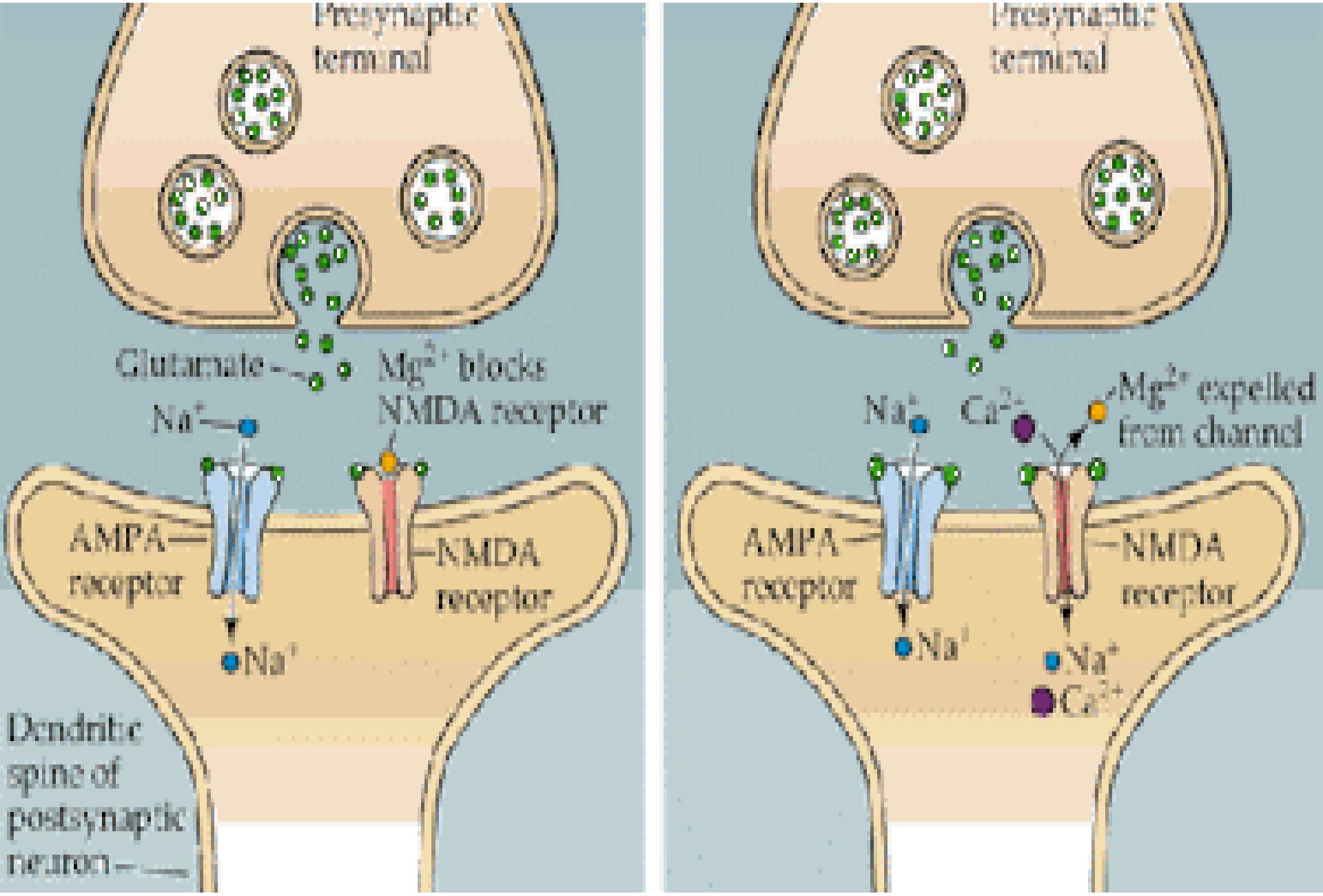


Figure 6.6 Glutamate synthesis and cycling between neurons and glia. The action of glutamate released into the synaptic cleft is terminated by uptake into neurons and surrounding glial cells via specific transporters. Within the nerve terminal, the glutamine released by glial cells and taken up by neurons is converted back to glutamate. Glutamate is transported into cells via excitatory amino acid transporters (EATTs) and loaded into synaptic vesicles via vesicular glutamate transporters (VGLUT).

L- GLUTAMATO

- VESICULAS TRANSPORTADORAS:

SOLO EN NEURONAS VGLUT1 Y VGLUT2


Presynaptic terminal
Glutamate
Mg^{2+} blocks NMDA receptor
Na^+
AMPA receptor
NMDA receptor
Na^+
Dendritic spine of postsynaptic neuron
Presynaptic terminal
Na^+
Ca^{2+}
Mg^{2+} expelled from channel
AMPA receptor
NMDA receptor
Na^+
Na^+
Ca^{2+}

L- GLUTAMATO

- 5 TRANSPORTADORES PARA GLUTAMATO

TRANSPORTADORES PARA AMINOACIDOS EXCITADORES (EAAT 1-5)

EAAT2: GLIA

EAAT1:CEREBELO Y GLIA

EAAT3: CORTEZA HIPOCAMPO CAUDADO

EAAT4: CEL. PURKINGE EN CEREBEL

EAAT5: RETINA

RE L- GLUTAMATO

- IONOTROPICOS:
  NMDA, AMPA, KAINATO
- METABOTROPICOS:(mGLUR)

ACOPLADOS A PROTEINA G

GRUPO I, II Y III 8 ISOTIPOS

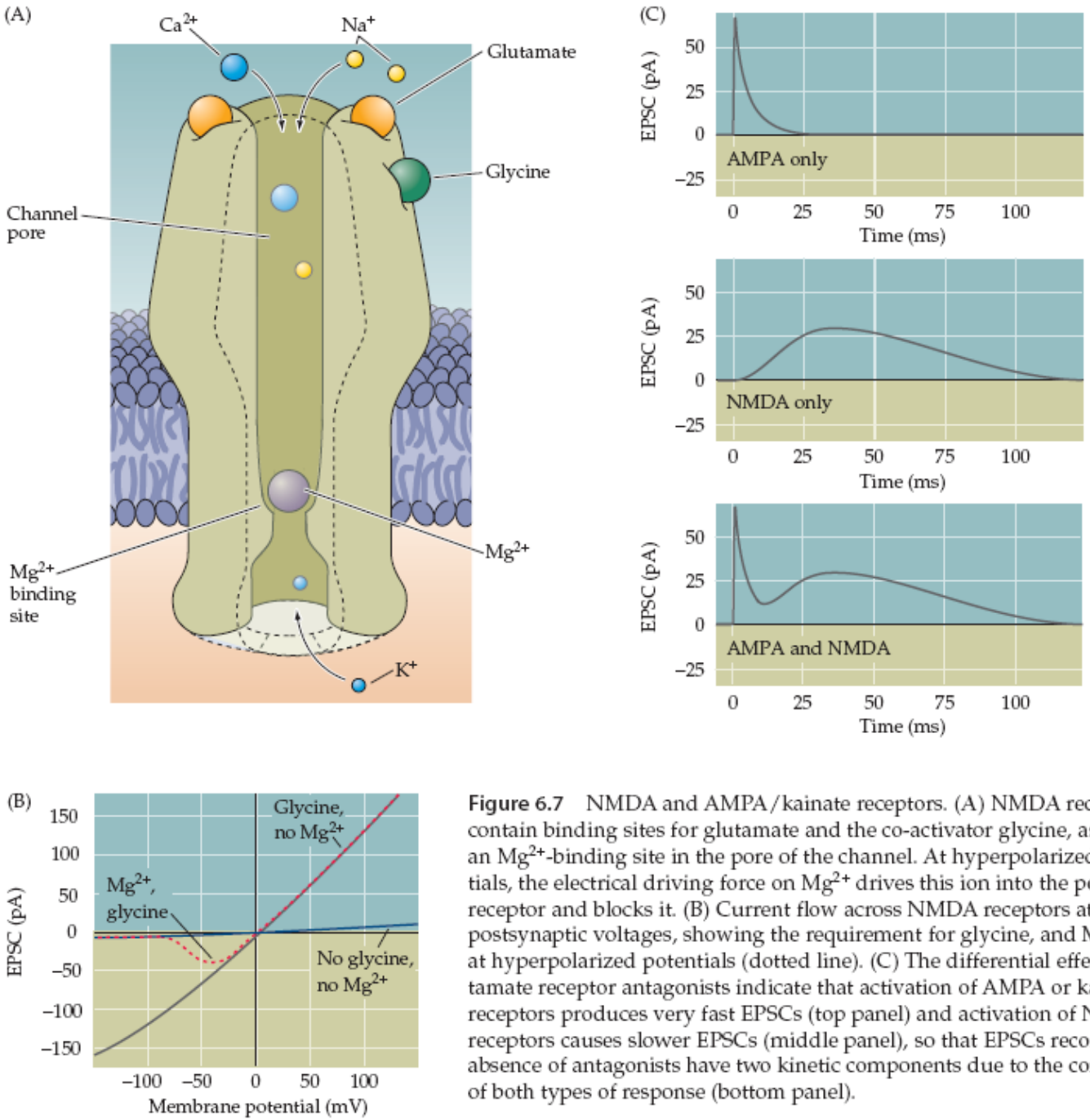
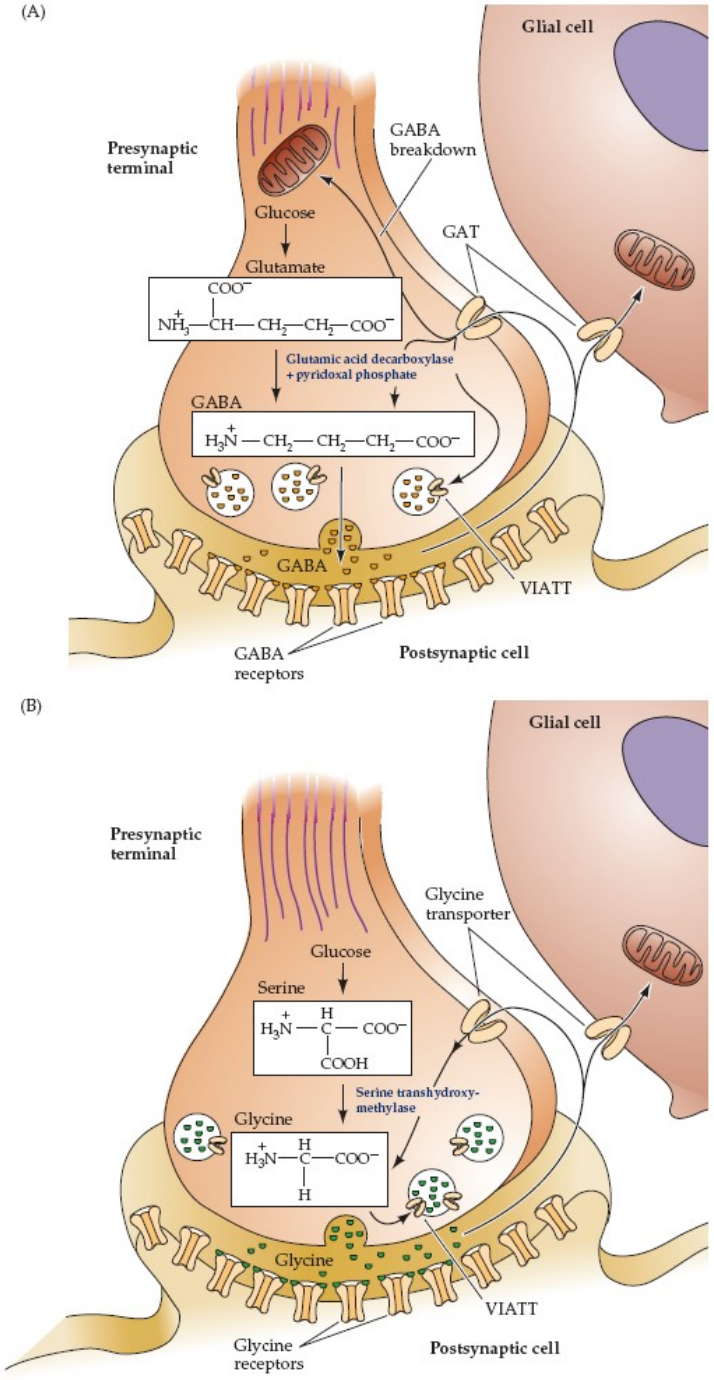


Figure 6.7 NMDA and AMPA/kainate receptors. (A) NMDA receptors contain binding sites for glutamate and the co-activator glycine, as well as an Mg^{2+}-binding site in the pore of the channel. At hyperpolarized potentials, the electrical driving force on Mg^{2+} drives this ion into the pore of the receptor and blocks it. (B) Current flow across NMDA receptors at a range of postsynaptic voltages, showing the requirement for glycine, and Mg^{2+} block at hyperpolarized potentials (dotted line). (C) The differential effects of glutamate receptor antagonists indicate that activation of AMPA or kainate receptors produces very fast EPSCs (top panel) and activation of NMDA receptors causes slower EPSCs (middle panel), so that EPSCs recorded in the absence of antagonists have two kinetic components due to the contribution of both types of response (bottom panel).

GABA

- MAYOR CONCENTRACION EN EL CEREBELO
- HACES GABAERGICOS ESTRIADO A SUSTANCIA NIGRA Y CEL. PURKINJE EMITEN A NUCLEO DORSAL VESTIBULAR Y

Figure 6.8 Synthesis, release, and reuptake of the inhibitory neurotransmitters GABA and glycine. (A) GABA is synthesized from glutamate by the enzyme glutamic acid decarboxylase, which requires pyridoxal phosphate. (B) Glycine can be synthesized by a number of metabolic pathways; in the brain, the major precursor is serine. High-affinity transporters terminate the actions of these transmitters and return GABA or glycine to the synaptic terminals for reuse, with both transmitters being loaded into synaptic vesicles via the vesicular inhibitory amino acid transporter (VIATT).



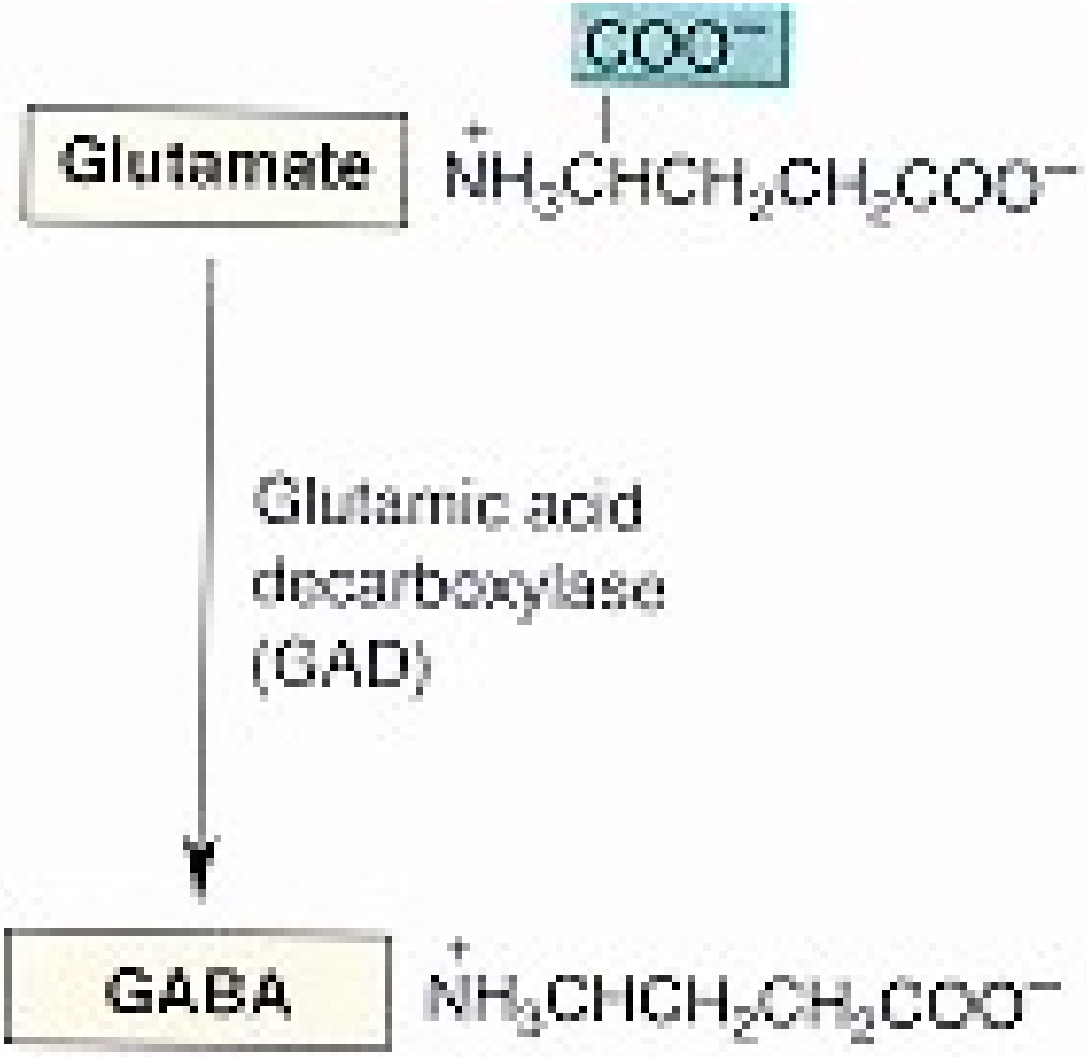
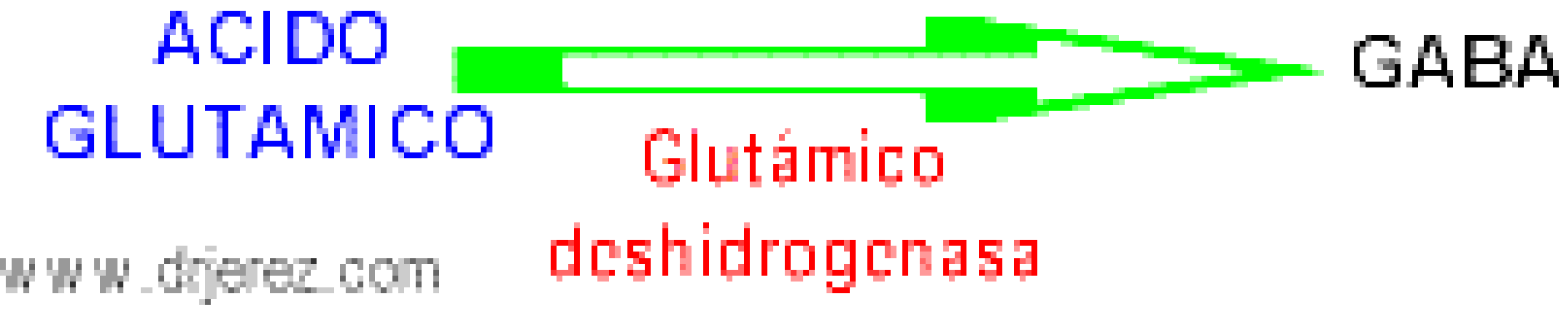
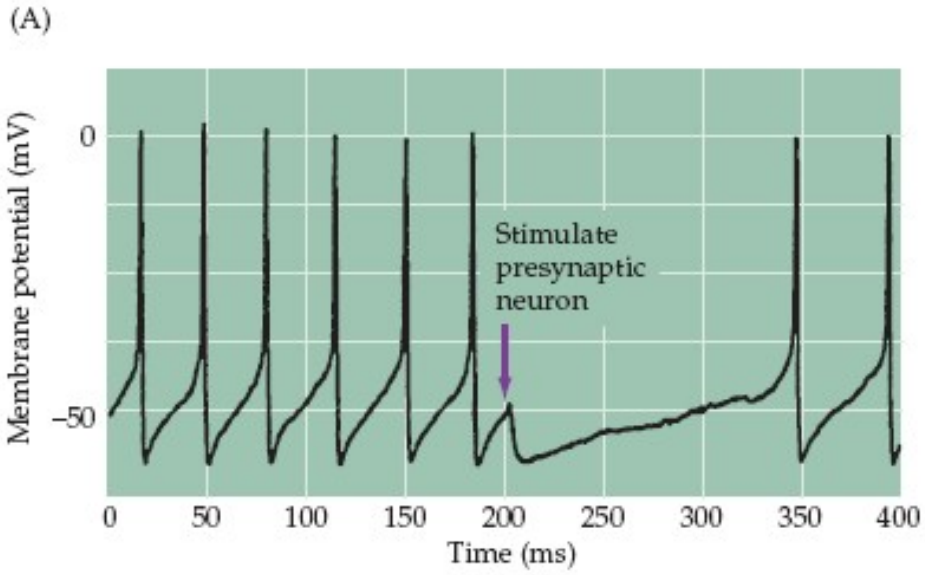


Figure 6.15
The synthesis of GABA from glutamate.


ACIDO
GLUTAMICO
Glutámico
deshidrogenasa
GABA
www.djerez.com

GABA

- PRECURSOR: GLUCOSA CON COFACTOR FOSFATO DE PIRIDOXAL DERIVA DE LA VIT B6
- TRANSPORTADOR VESICULAR GAT CONVIERTEN A SUCCINATO DEGRADADO POR LA GABA TRANSAMINASA Y SUCCINICO ALDEHIDO DESHIDROGENASA
- Y HIDROXIBUTIRATO



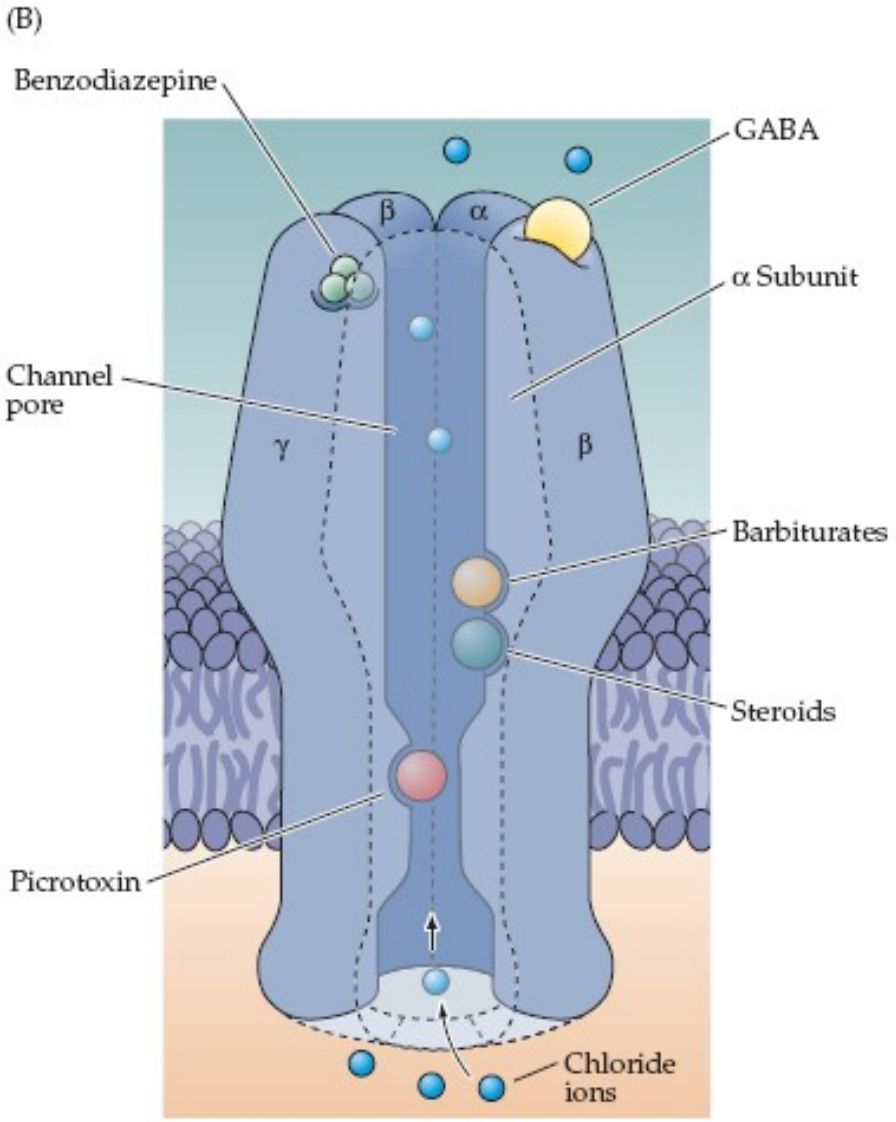
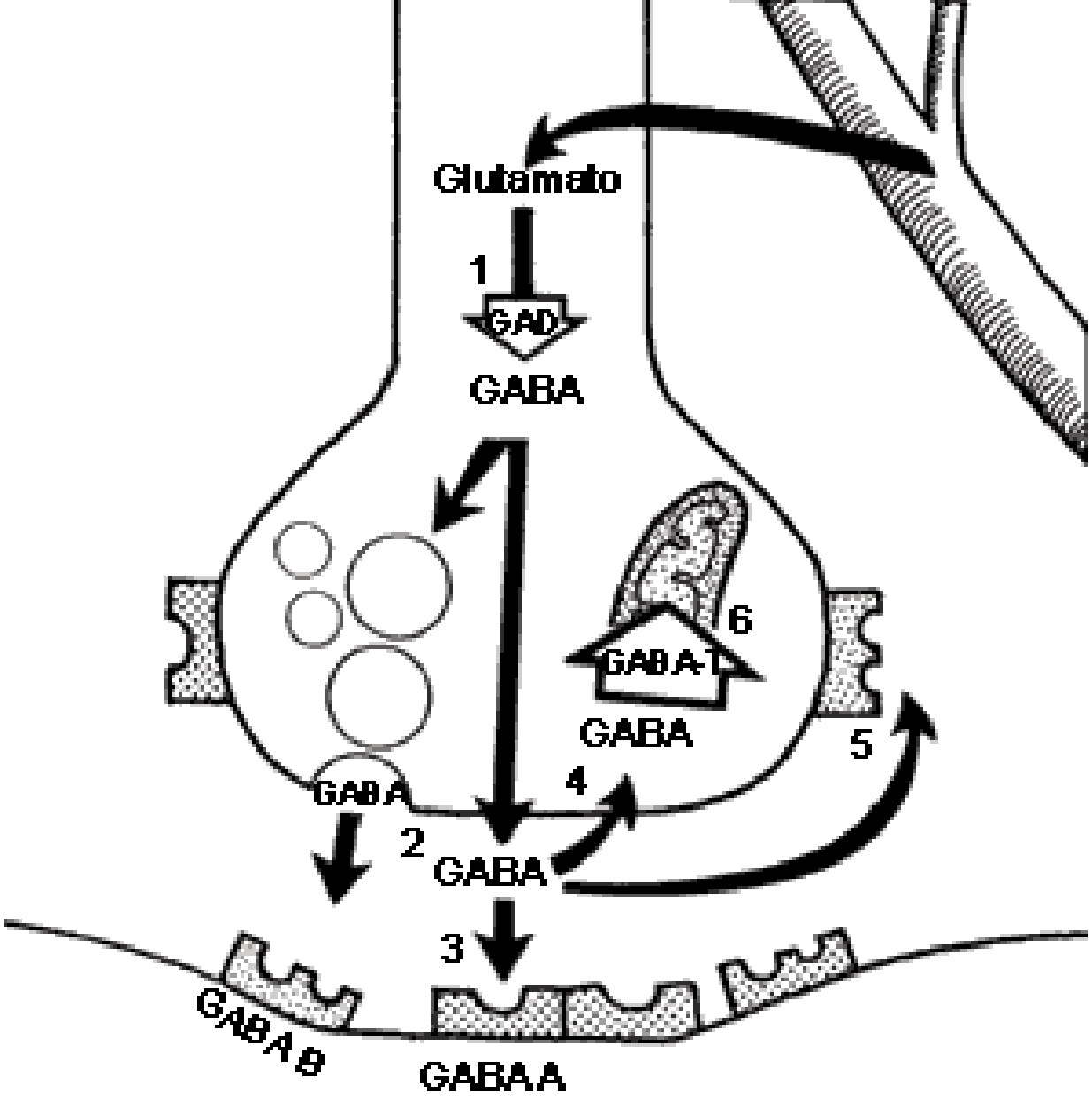
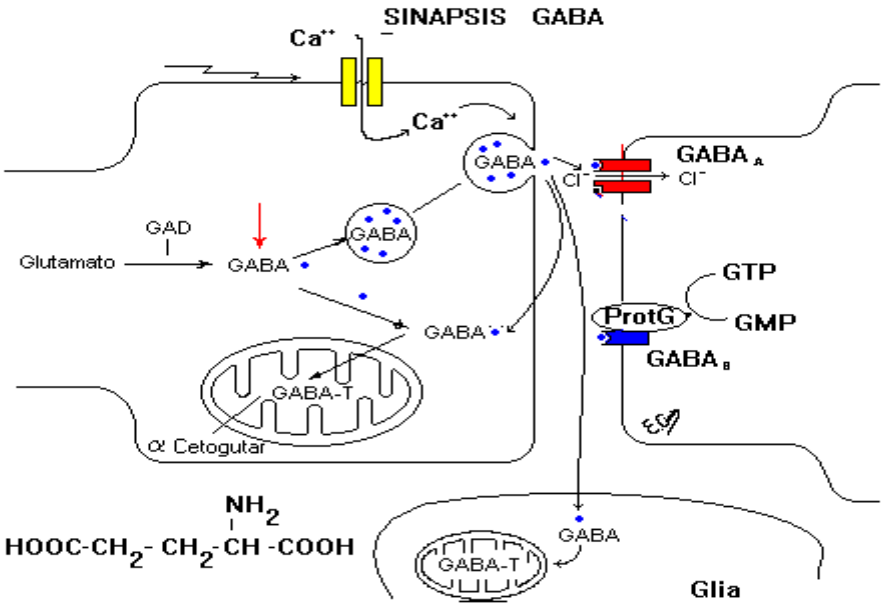


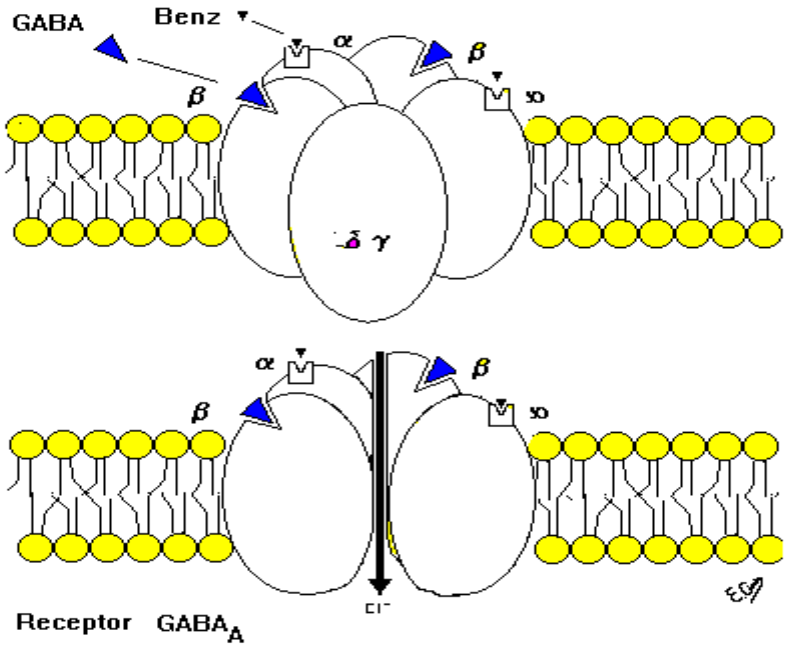
Figure 6.9 Ionotropic GABA receptors. (A) Stimulation of a presynaptic GABAergic interneuron, at the time indicated by the arrow, causes a transient inhibition of action potential firing in its postynaptic target. This inhibitory response is caused by activation of postsynaptic $GABA_A$ receptors. (B) Ionotropic GABA receptors contain two binding sites for GABA and numerous sites at which drugs bind to and modulate these receptors. (A after Chavas and Marty, 2003).

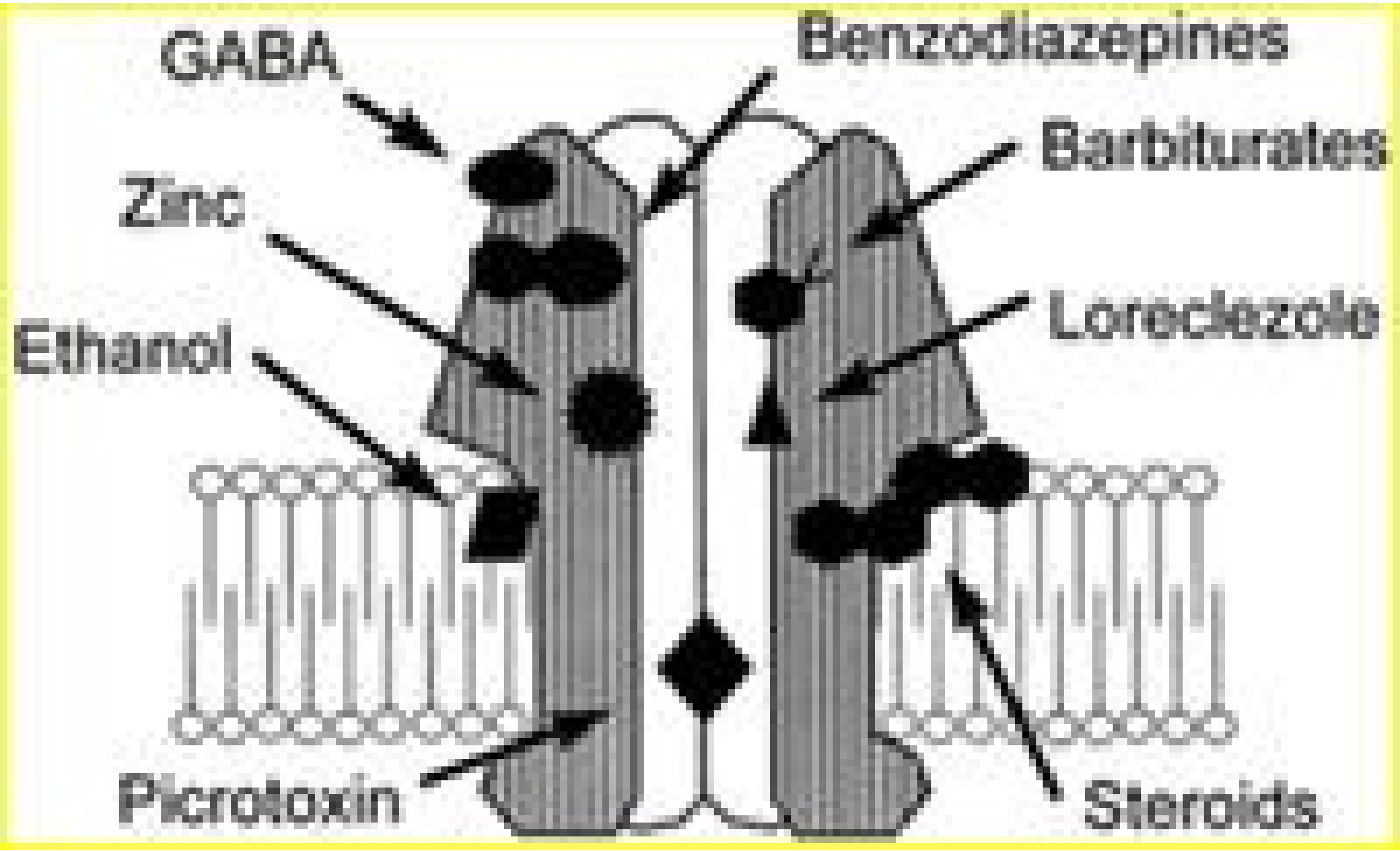
RE GABA

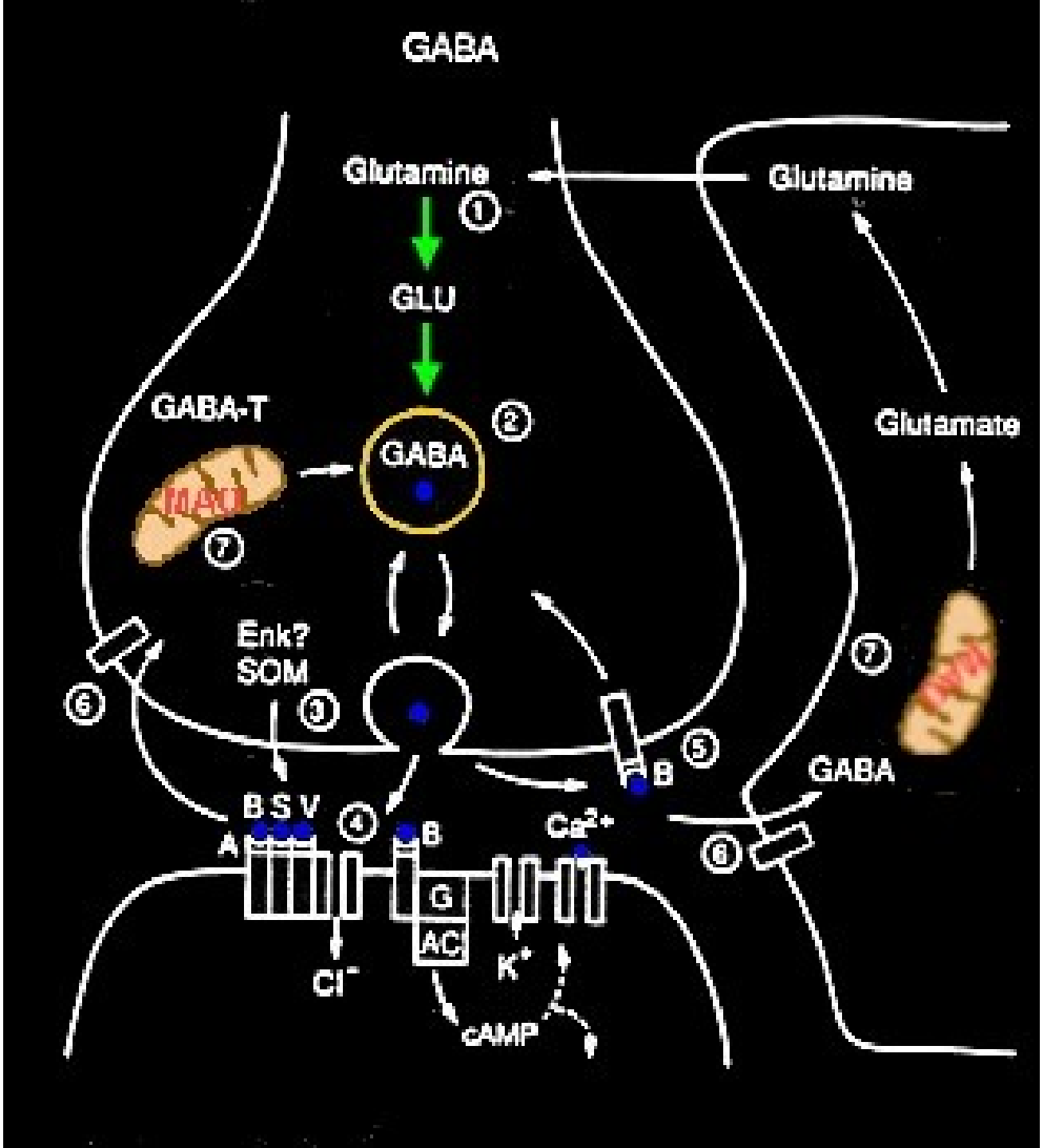
- GABA A IONOTROPICO PERMEABLE A CLORO, BZD
- GABA B METABOTROPICO PERMEABLE A K, BLOQUEO DE CANALES DE CA . R1-R2
- GABA C IONOTROPICOS


Glutamato
1
GAD
GABA
6
GABA-T
GABA
5
GABA
4
2
GABA
3
GABA B
GABA A


SINAPSIS GABA
Ca++
Ca++
GABA
GABA A
Cl-
Cl-
GAD
Glutamato
GABA
GABA
GABA
GTP
ProtG
GMP
GABA B
GABA-T
α Cetogutar
NH2
HOOC-CH2- CH2-CH -COOH
GABA
GABA-T
Glia

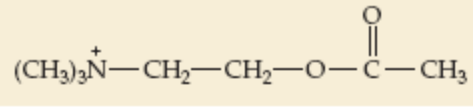

GABA
Benz
α
β
β
ɔ
δ γ
α
β
β
ɔ
Cl-
Receptor GABAA


GABA
Benzodiazepines
Barbiturates
Zinc
Loreclezole
Ethanol
Picrotoxin
Steroids


GABA
Glutamine
Glutamine
GLU
GABA-T
GABA
Glutamate
Enk?
SOM
B S V
A
B
G
AC
Ca^{2+}
Cl^-
K^+
cAMP
GABA
B

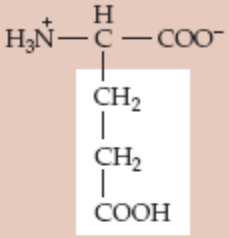
SMALL-MOLECULE NEUROTRANSMITTERS

Acetylcholine

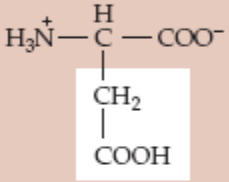


AMINO ACIDS

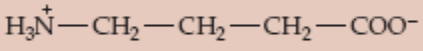
Glutamate



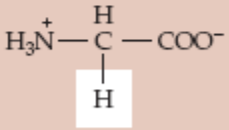
Aspartate

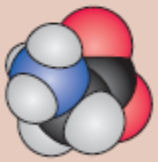


GABA



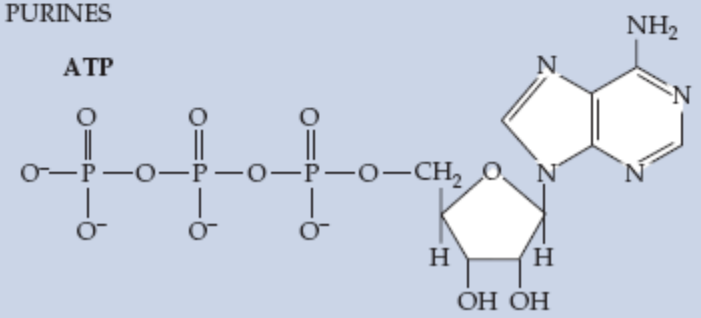
Glycine





PURINES

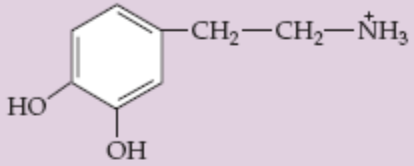
ATP



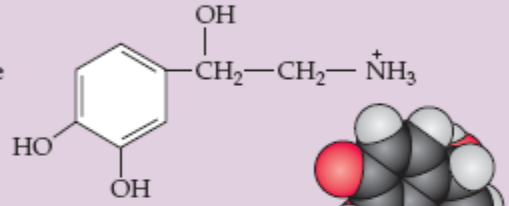
BIOGENIC AMINES

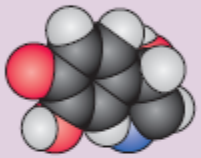
CATECHOLAMINES

Dopamine

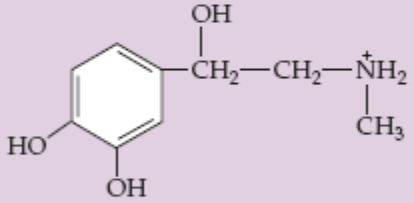


Norepinephrine



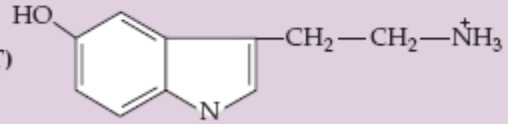


Epinephrine



INDOLEAMINE

Serotonin (5-HT)



IMIDAZOLEAMINE

Histamine

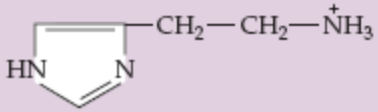


TABLE 6.1
Functional Features of the Major Neurotransmitters

Neurotransmitter	*Postsynaptic effect*[a]	*Precursor(s)*	*Rate-limiting step in synthesis*	*Removal mechanism*	*Type of vesicle*
ACh	Excitatory	Choline + acetyl CoA	CAT	AChEase	Small, clear
Glutamate	Excitatory	Glutamine	Glutaminase	Transporters	Small, clear
GABA	Inhibitory	Glutamate	GAD	Transporters	Small, clear
Glycine	Inhibitory	Serine	Phosphoserine	Transporters	Small, clear
Catecholamines (epinephrine, norepinephrine, dopamine)	Excitatory	Tyrosine	Tyrosine hydroxylase	Transporters, MAO, COMT	Small dense-core, or large irregular dense-core
Serotonin (5-HT)	Excitatory	Tryptophan	Tryptophan hydroxylase	Transporters, MAO	Large, dense-core
Histamine	Excitatory	Histidine	Histidine decarboxylase	Transporters	Large, dense-core
ATP	Excitatory	ADP	Mitochondrial oxidative phosphor-ylation; glycolysis	Hydrolysis to AMP and adenosine	Small, clear
Neuropeptides	Excitatory and inhibitory	Amino acids (protein synthesis)	Synthesis and transport	Proteases	Large, dense-core
Endocannabinoids	Inhibits inhibition	Membrane lipids	Enzymatic modification of lipids	Hydrolasis by FAAH	None
Nitric oxide	Excitatory and inhibitory	Arginine	Nitric oxide synthase	Spontaneous oxidation	None

[a]The most common postsynaptic effect is indicated; the same transmitter can elicit postsynaptic excitation or inhibition depending on the nature of the ion channels affected by transmitter binding (see Chapter 7).

ACETILCOLINA

- OTTO LOEWI 1921 NT DEL S. PARASIMPATICO
- 8 GRUPOS DE NEURONAS COLINERGICAS:

*Ch1-SEPTO MEDIAL

*Ch2-NUCLEO VERTICAL DE LA BANDA DIAGONAL

*Ch3-EXTREMO HORIZONTAL DE LA BANDA DIAGONAL

*Ch4- NUCLEO BASAL DE MEYNERT 90%-200000 N

*Ch5- NUCLEO PEDUNCULO PONTINO

*Ch6- NUCLEO DEL TEGMENTO DORSOLATERAL

*Ch7- NUCLEO MEDIAL DE LA HABENULA

*Ch8- NUCLEO PARABIGEMINAL

ACETILCOLINA

- INERVACION COLINERGICA:

HIPOCAMPO, AMIGDALA, CORTEZA ENTORRINAL III Y V CAPAS DE RE COLINERGICOS

Ach DISMINUYE CONDUCTIVIDAD DEL K+ SON SUSCEPTIBLES A INFLUENCIAS EXCITATORIAS

Ach CORTICAL INH. POR RE M2 O M4 O POR INTERNEURONAS GABAERGICAS.

FUNCIONES: PASO DE SUEÑO A VIGILIA Y MEMORIA

ACETILCOLINA

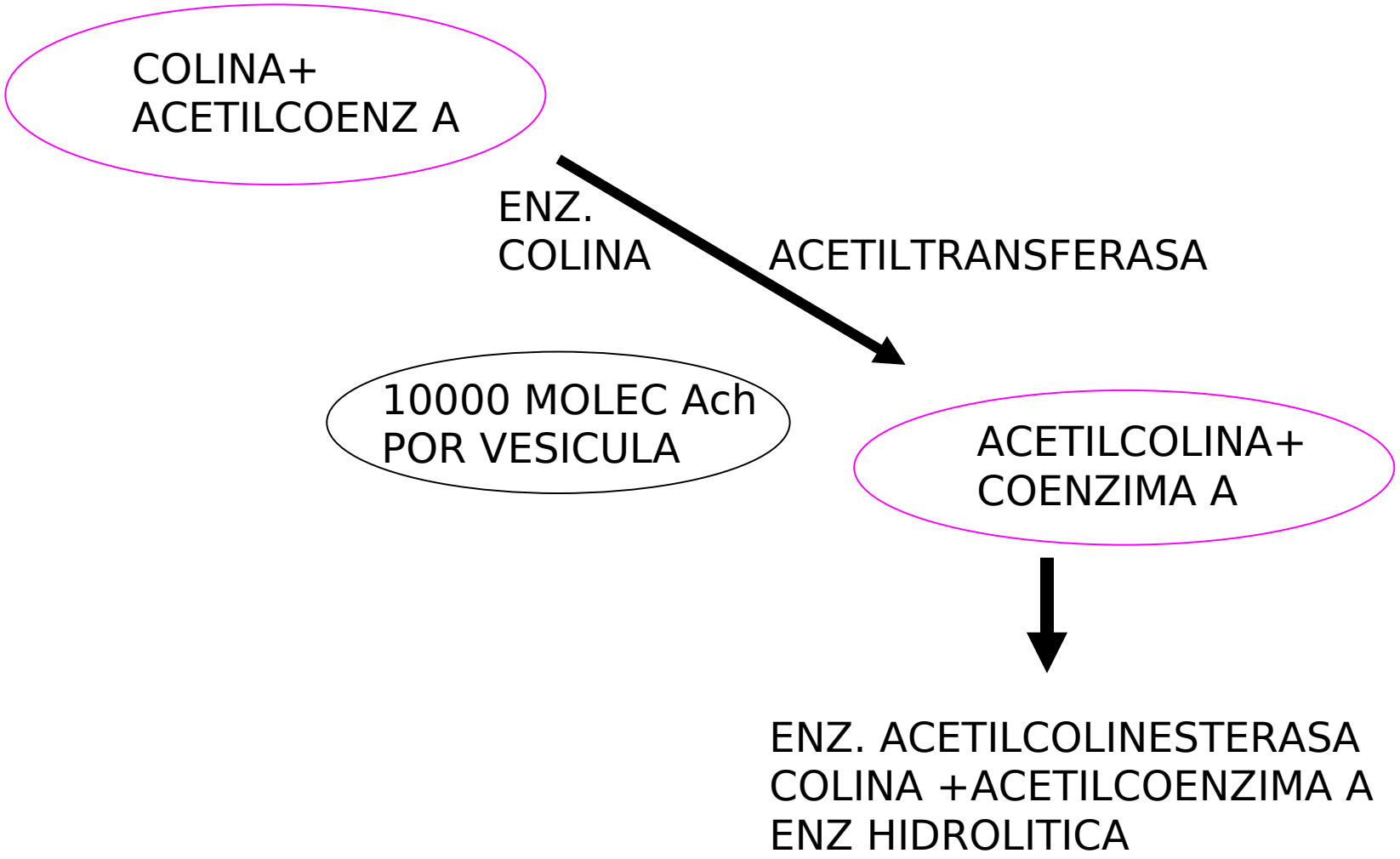
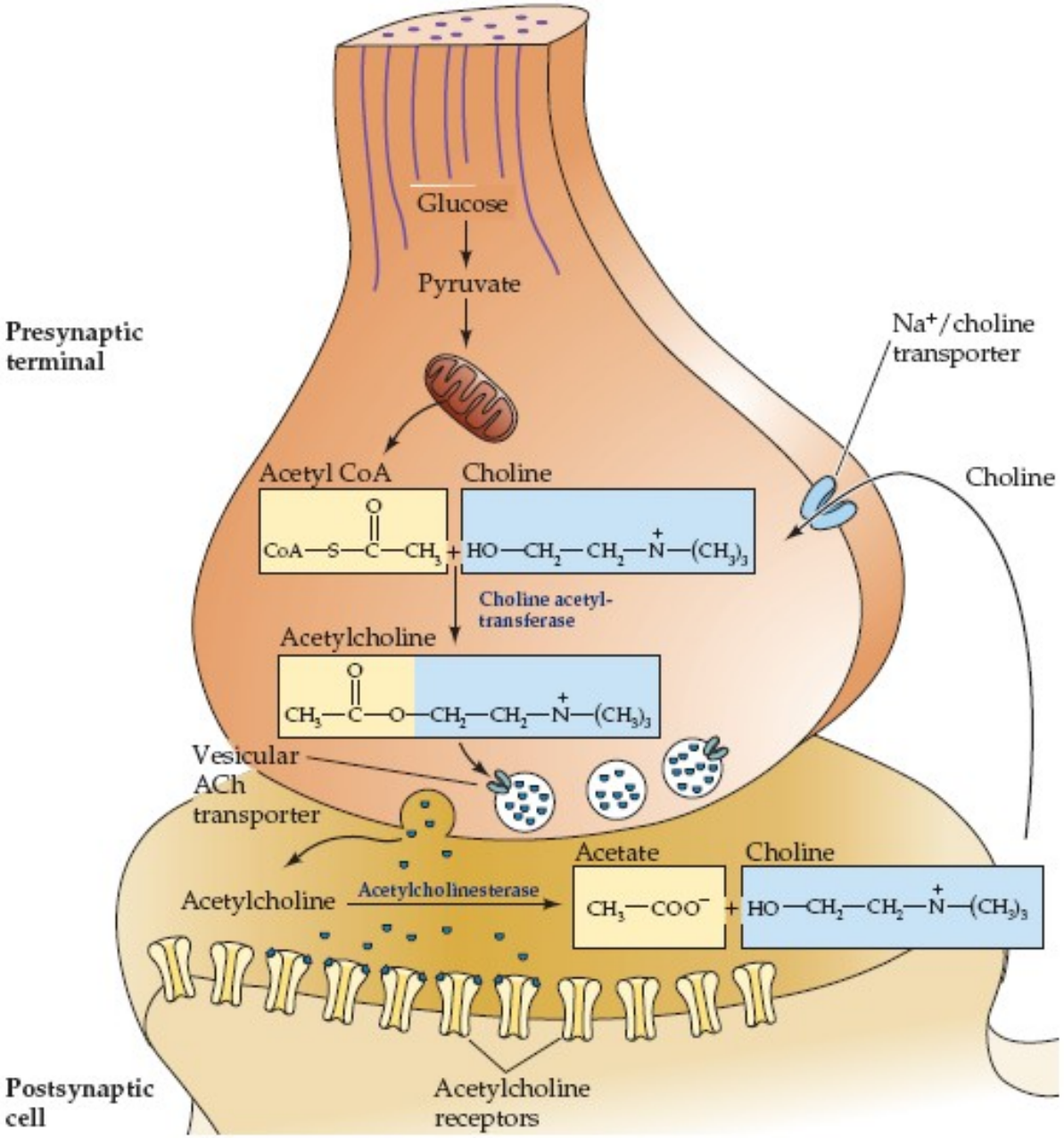
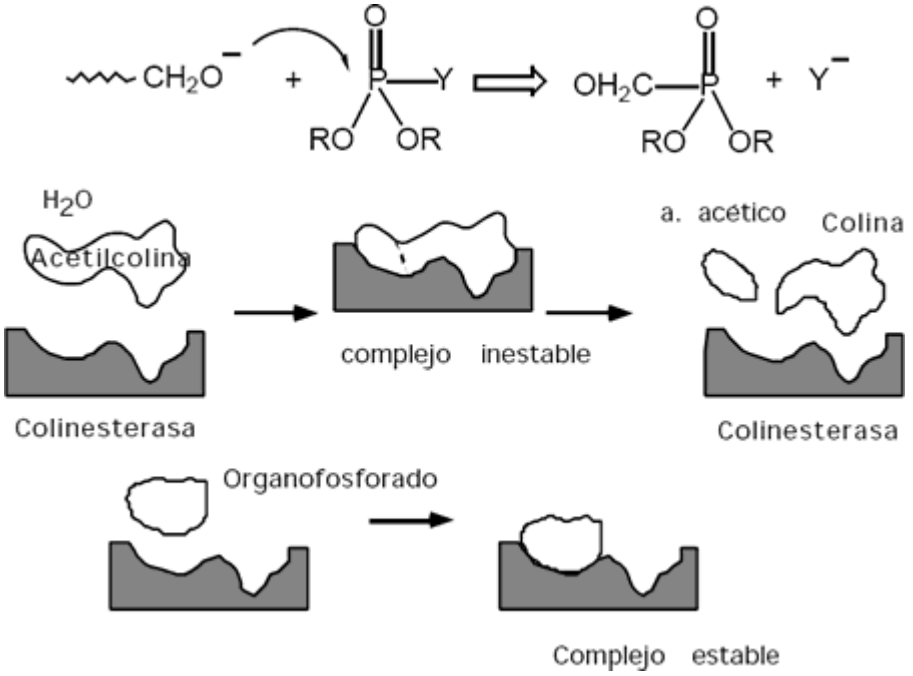


Figure 6.2 Acetylcholine metabolism in cholinergic nerve terminals. The synthesis of acetylcholine from choline and acetyl CoA requires choline acetyltransferase. Acetyl CoA is derived from pyruvate generated by glycolysis, while choline is transported into the terminals via a Na^+-dependent transporter. Acetylcholine is loaded into synaptic vesicles via a vesicular transporter. After release, acetylcholine is rapidly metabolized by acetylcholinesterase, and choline is transported back into the terminal.

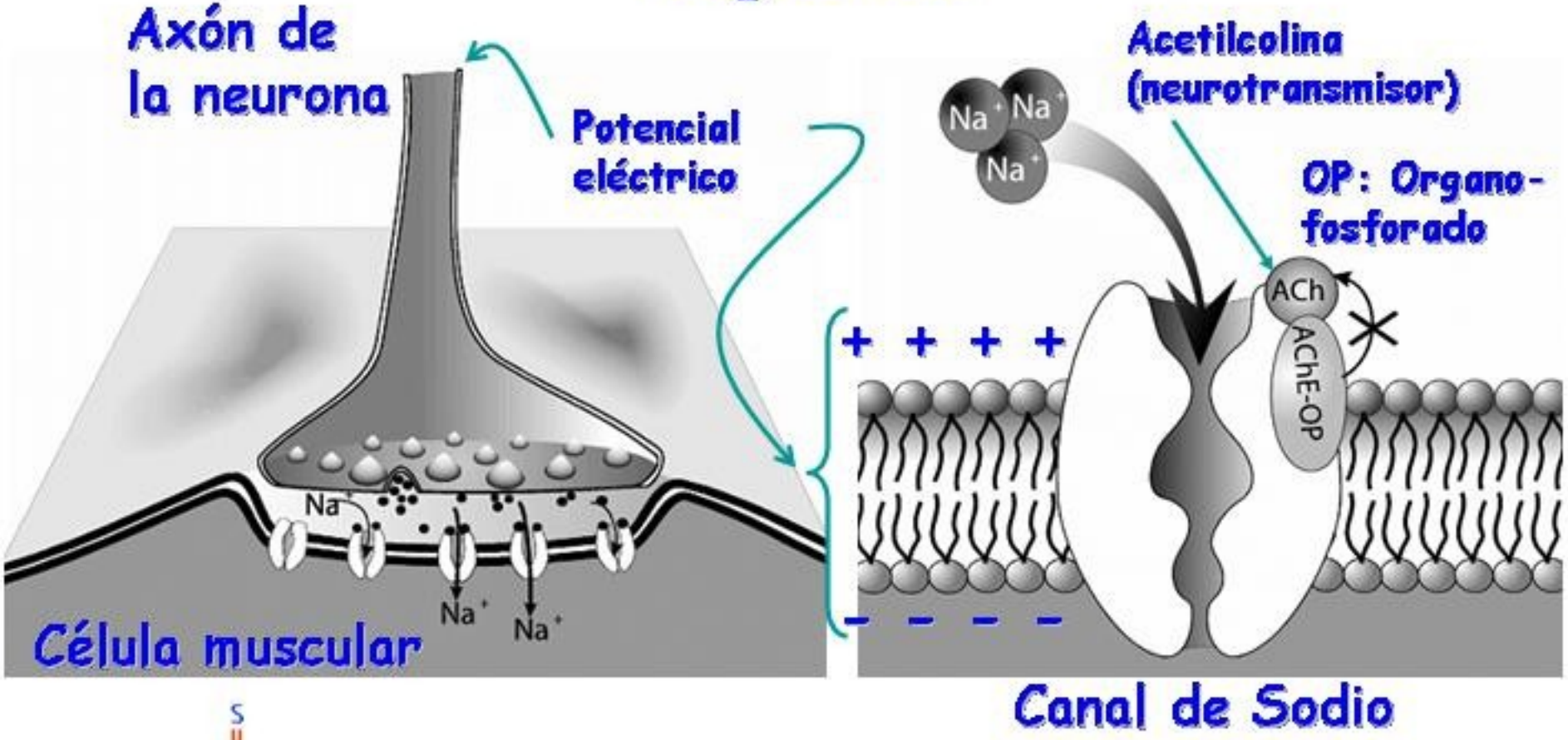


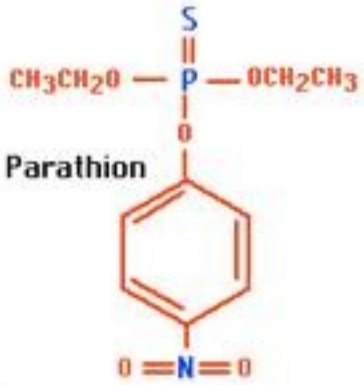
ACETILCOLINA

ORGANOFOSFORADOS AGONISTAS DE LA ENZIMA ACETILCOLINESTERASA DE LA DEGRADACION



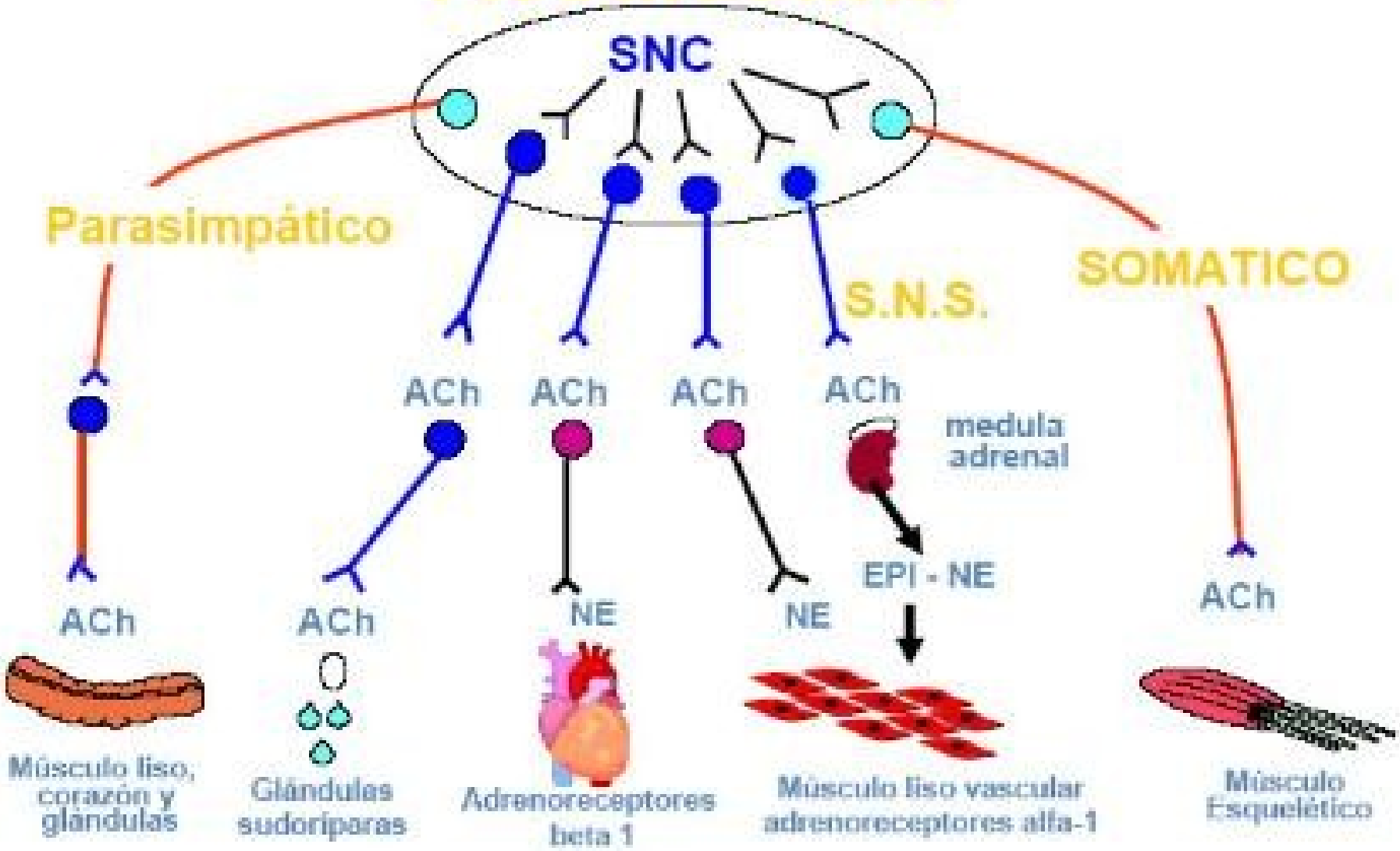
Plaguicidas





Inhibición de la función de la sinapsis neuromuscular por organofosforados

Acetilcolina



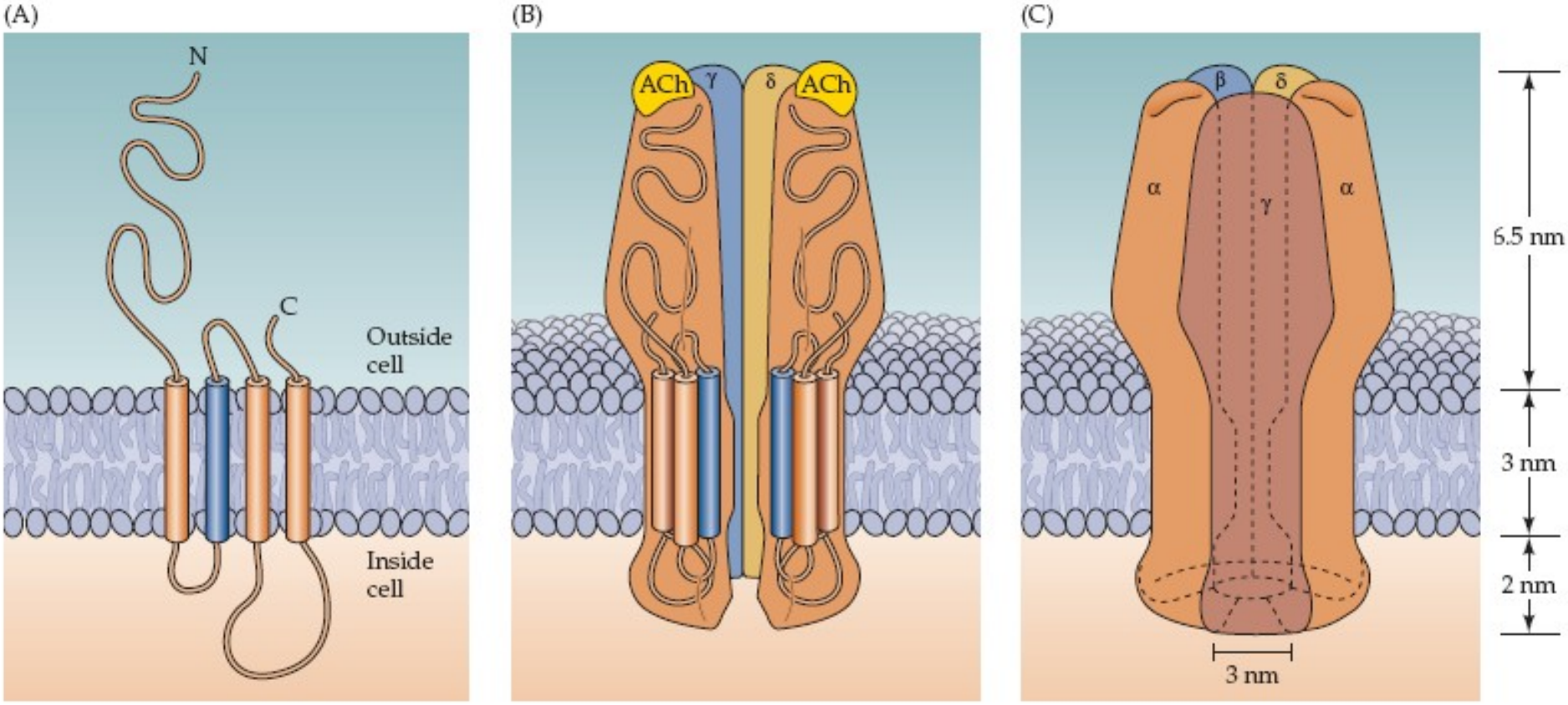
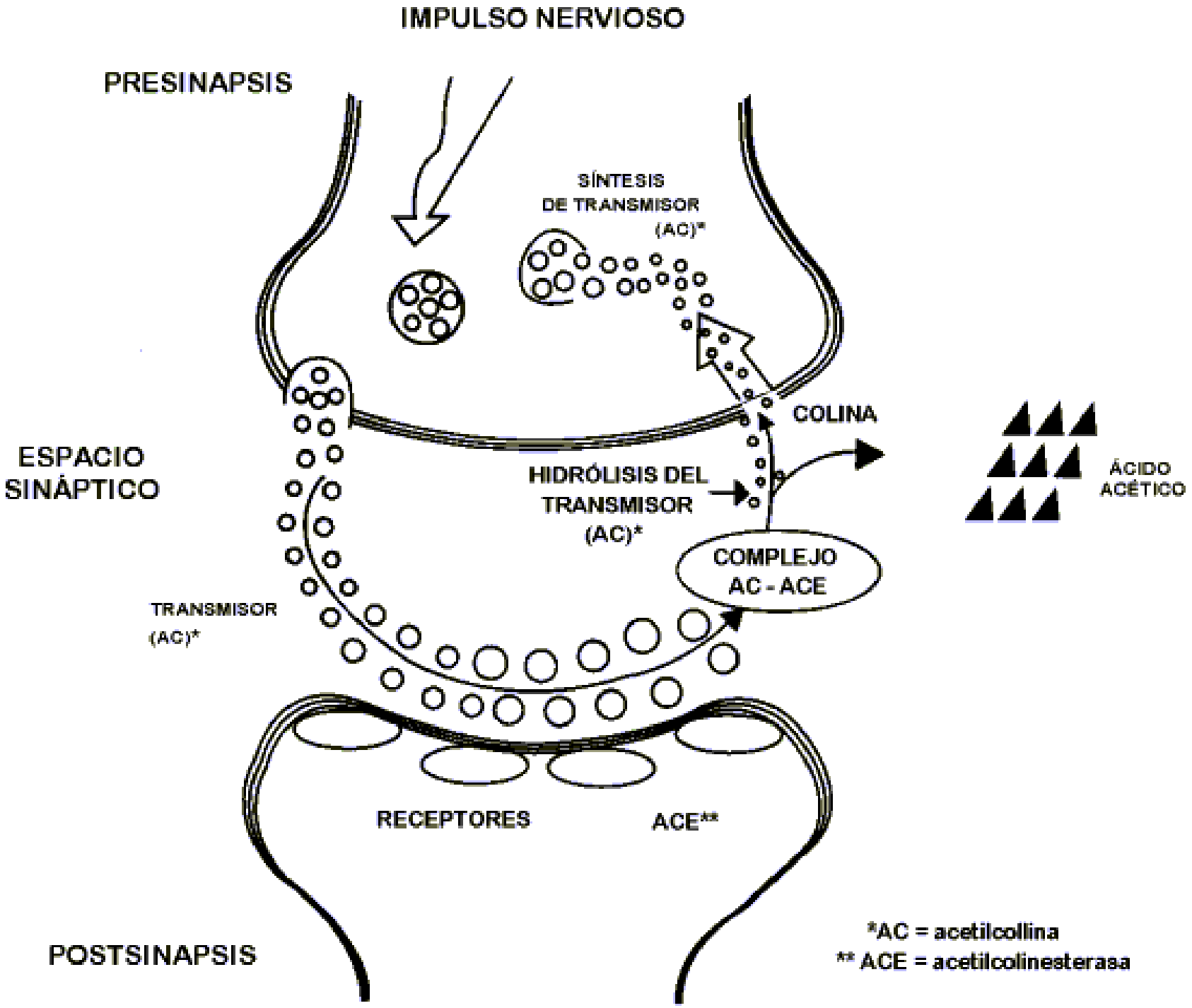


Figure 6.3 The structure of the nACh receptor/channel. (A) Each receptor subunit crosses the membrane four times. The membrane-spanning domain that lines the pore is shown in blue. (B) Five such subunits come together to form a complex structure containing 20 transmembrane domains that surround a central pore. (C) The openings at either end of the channel are very large—approximately 3 nm in diameter; even the narrowest region of the pore is approximately 0.6 nm in diameter. By comparison, the diameter of Na^+ or K^+ is less than 0.3 nm.


IMPULSO NERVIOSO
PRESINAPSIS
SÍNTESIS
DE TRANSMISOR
(AC)*
COLINA
ESPACIO
SINÁPTICO
HIDRÓLISIS DEL
TRANSMISOR
(AC)*
ÁCIDO
ACÉTICO
COMPLEJO
AC - ACE
TRANSMISOR
(AC)*
RECEPTORES
ACE**
POSTSINAPSIS
*AC = acetilcollina
** ACE = acetilcolinesterasa

RE COLINERGICOS

- RE NICOTINICOS: FIJAN NICOTINA Y A-BUNGAROTOXINA (VENENO DE SERPIENTE). IONOTROPICOS 5 SUBUNIDADES.
- RE MUSCARINICOS (amanita muscaria)

TEJ CARDIACO, MUSC. LISO Y GLAND EXOCRINAS Y SNC. METABOTROPICOS ACOPLADOS A PROT G. 5 SUBTIPOS M1-M5

- ATROPINA ANTAGONISTA DE RE
- 7 REGIONES TRANSMEMBRANA

RE MUSCARINICOS M1

LOCALIZACION: HIPOCAMPO CORTEZA, ESTRIADO, TUBERCULO OLFATORIO, CEREBRO MEDIO, GANGLIOS AUTONOMOS.

2 MENSAJERO IP3, DAG

ANTAGONISTA SELECTIVOS: PIRENZEPINA

RE MUSCARINICOS M2

LOCALIZACION: CEREBELO, TRONCO DEL ENCEFALO Y CEREBRO MEDIO, TUBERCULO OLFATORIO, HIPOCAMPO, CORAZON, MUSCULO LISO

2 MENSAJERO: AMPc, CANAL DE K+, CANAL DE CA++

ANTAGONISTAS SELECTIVOS: AF DX384

N-[2-[2-[(Dipropylamino)methyl]-1-piperidinyl]ethyl]-5,6 -dihydro-6-oxo-11H-pyrido[2,3-b][1,4]benzodiazepine-11-carboxamide

RE MUSCARINICOS M3

LOCALIZACION: HIPOCAMPO, CORTEZA, ESTRIAADO Y GLAN.EXOCRINAS

2 MENSAJERO: IP3,

DAG (DIACILGLICEROL)

ANTAGONISTA: 4- DAMP

4-diphenyl-acetoxy-N-methyl-piperidine

RE MUSCARINICOS M4

LOCALIZACION: ESTRIADO, TUBERCULO OLFATORIO, HIPOCAMPO, CORTEZA, HIPOCAMPO Y PULMON

2 MENSAJERO: AMPc, CANAL DE K+, CANAL DE CA++

RE MUSCARINICOS M5

LOCALIZACION: MUY BAJA DENSIDAD EN MULTIPLES REGIONES.

2 MENSAJERO: IP3,

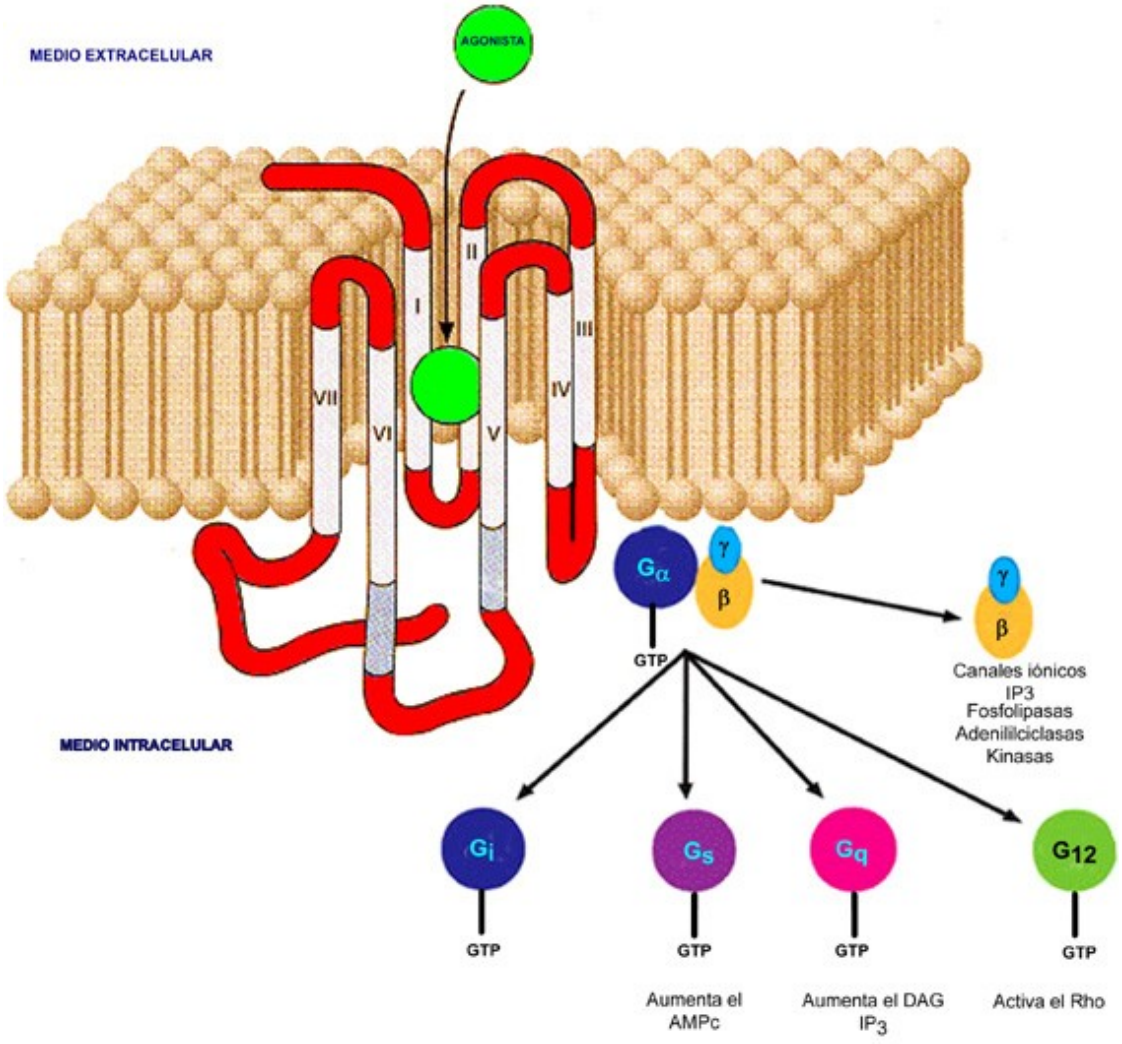
DAG (DIACILGLICEROL)

(A)

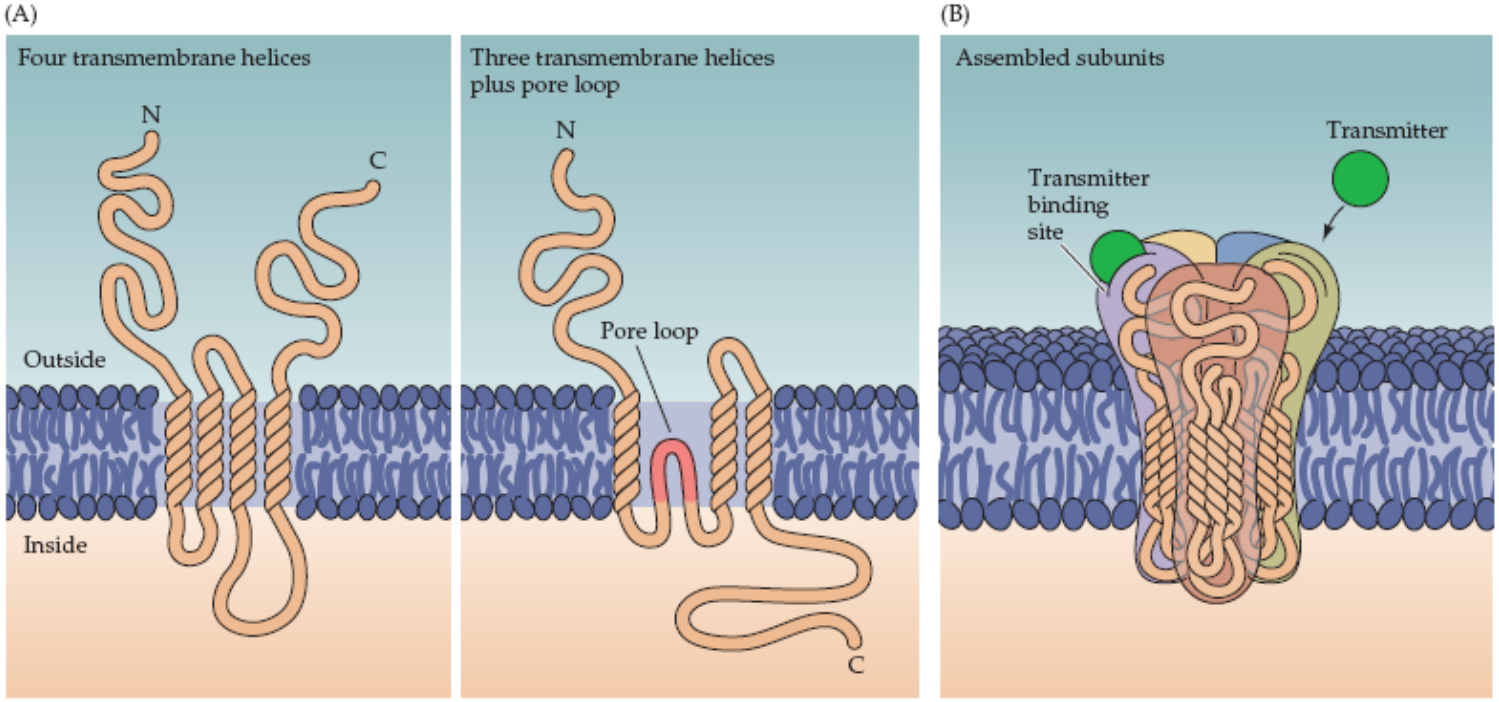
(B)

(C)

(A) The banded krait *Bungarus multicinctus*. (B) A marine cone snail (*Conus* sp.) uses venomous darts to kill a small fish. (C) Betel nuts, *Areca catechu*, growing in Malaysia. (A, Robert Zappalorti/Photo Researchers, Inc.; B, Zoya Maslak and Baldomera Olivera, University of Utah; C, Fletcher Baylis/Photo Researchers, Inc.)



ESTRUCTURA DE LOS RECEPTORES MUSCARÍNICOS



(C)

Receptor	AMPA	NMDA	Kainate	GABA	Glycine	nACh	Serotonin	Purines
Subunits (combination of 4 or 5 required for each receptor type)	Glu R1	NR1	Glu R5	α_{1-7}	α1	α_{2-9}	5-HT_3	P_{2X1}
	Glu R2	NR2A	Glu R6	β_{1-4}	α2	β_{1-4}		P_{2X2}
	Glu R3	NR2B	Glu R7	γ_{1-4}	α3	γ		P_{2X3}
	Glu R4	NR2C	KA1	δ	α4	δ		P_{2X4}
		NR2D	KA2	ε	β			P_{2X5}
				ρ_{1-3}				P_{2X6}
								P_{2X7}

Figure 6.4 The general architecture of ligand-gated receptors. (A) One of the subunits of a complete receptor. The long N-terminal region forms the ligand-binding site, while the remainder of the protein spans the membrane either four times (left) or three times (right). (B) Assembly of either four or five subunits into a complete receptor. (C) A diversity of subunits come together to form functional ionotropic neurotransmitter receptors.

(A)

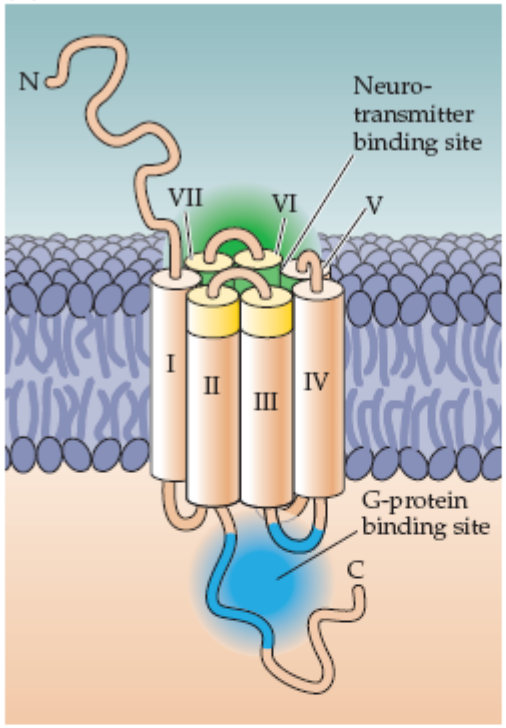


Figure 6.5 Structure and function of metabotropic receptors. (A) The transmembrane architecture of metabotropic receptors. These monomeric proteins contain seven transmembrane domains. Portions of domains II, III, VI, and VII make up the neurotransmitter-binding region. G-proteins bind to both the loop between domains V and VI and to portions of the C-terminal region. (B) Varieties of metabotropic neurotransmitter receptors.

(B)

Receptor class	Glutamate	$GABA_B$	Dopamine	NE, Epi	Histamine	Serotonin	Purines	Muscarinic
Receptor subtype	Class I	$GABA_B$ R1	$D1_A$	α1	H1	5-HT 1	A type	M1
	mGlu R1	$GABA_B$ R2	$D1_B$	α2	H2	5-HT 2	A1	M2
	mGlu R5		D2	β1	H3	5-HT 3	A2a	M3
	Class II		D3	β2		5-HT 4	A2b	M4
	mGlu R2		D4	β3		5-HT 5	A3	M5
	mGlu R3					5-HT 6	P type	
	Class III					5-HT 7	P2x	
	mGlu R4						P2y	
	mGlu R6						P2z	
	mGlu R7						P2t	
	mGlu R8						P2u	

CATECOLAMINAS

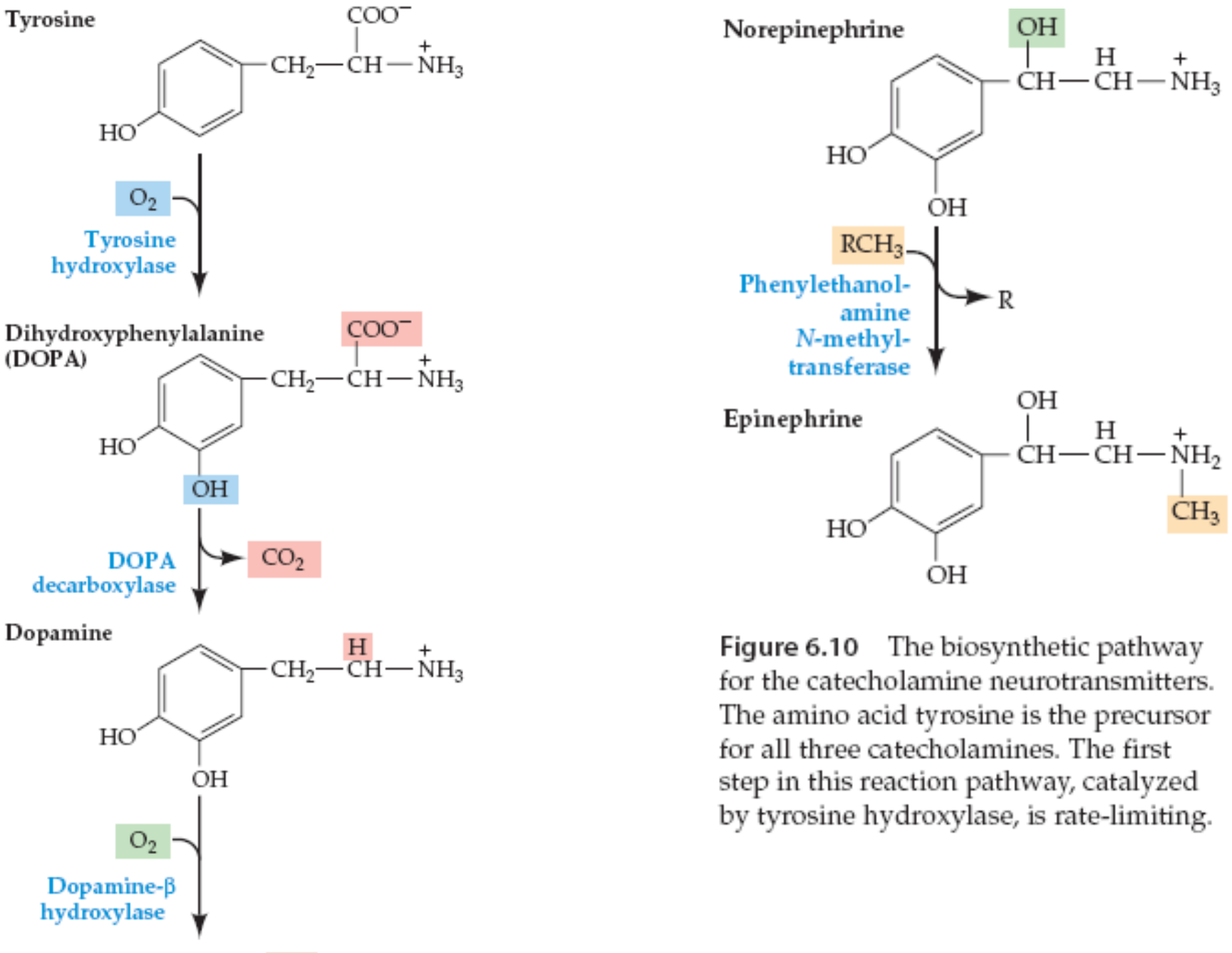


Figure 6.10 The biosynthetic pathway for the catecholamine neurotransmitters. The amino acid tyrosine is the precursor for all three catecholamines. The first step in this reaction pathway, catalyzed by tyrosine hydroxylase, is rate-limiting.

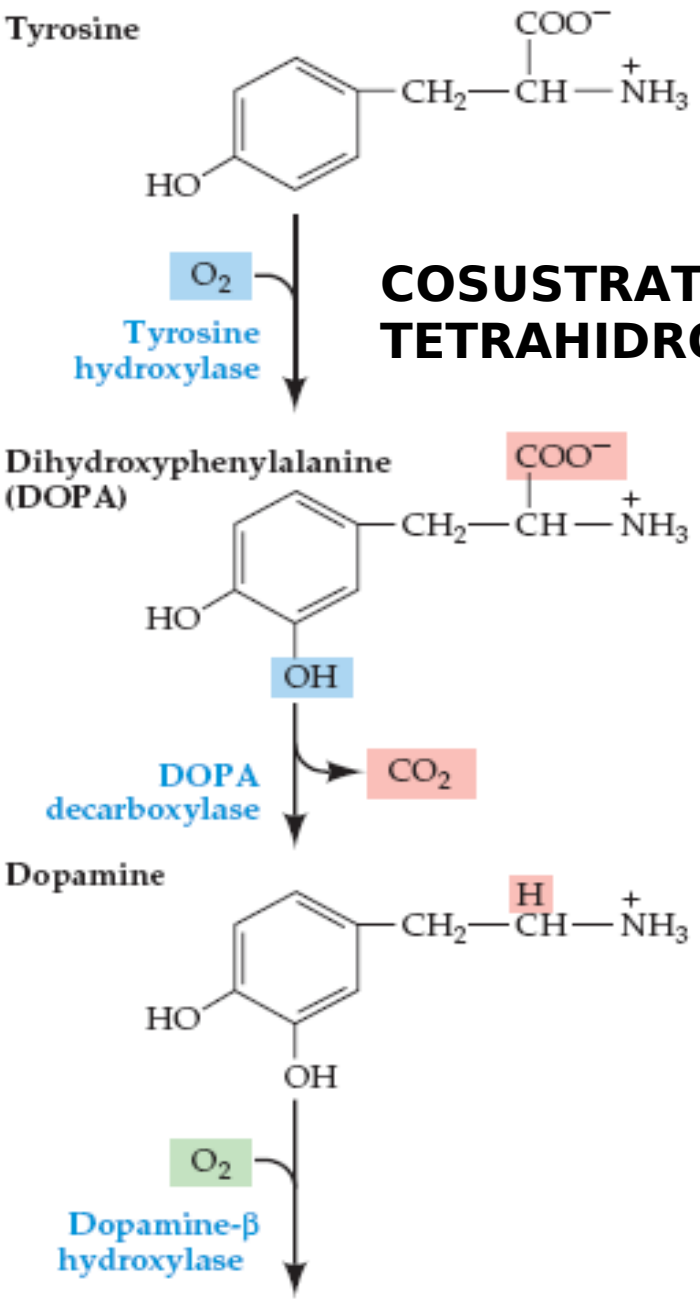
DOPAMINA

UBICADA PRINCIPALMENTE EN EL CUERPO ESTRIADO

FUNCION: COORDINACION DE MOVIMIENTOS CORPORALES, MOTIVACION, RECOMPENSA Y REFUERZO

DOPAMINA

- TRANSPORTADOR VESICULAR DE MONOAMINAS
- RECAPTACION DE LA DOPAMINA POR EL TRANPOSRTADOR DE DOPAMINA NA+ DEPENDIENTE (DAT)
- ENZIMAS DE CATABOLISMO: MAO COMT (CATECOL O METIL TRANSFERASA MITOCONDRIAL Y CITOPLASMA)
- FENELZINA Y TRANILCIPROMINA ANTIDEPRESIVOS



COSUSTRATO: TETRAHIDROBIOPTERINA

VIAS CEREBRALES DOPAMINERGICAS

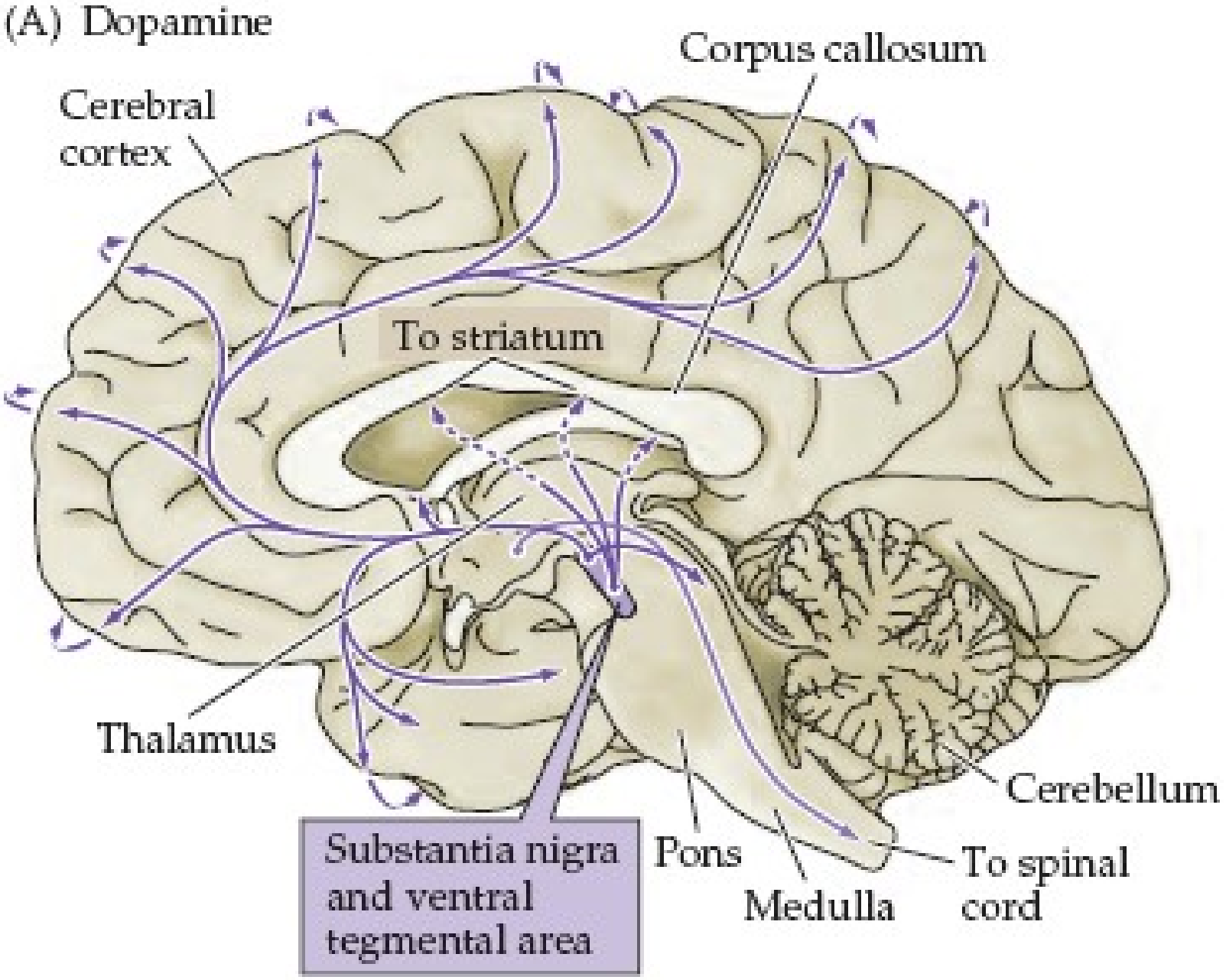
- NIGROESTRIATAL 80%
- MESOLIMBICA
- MESOCORTICAL

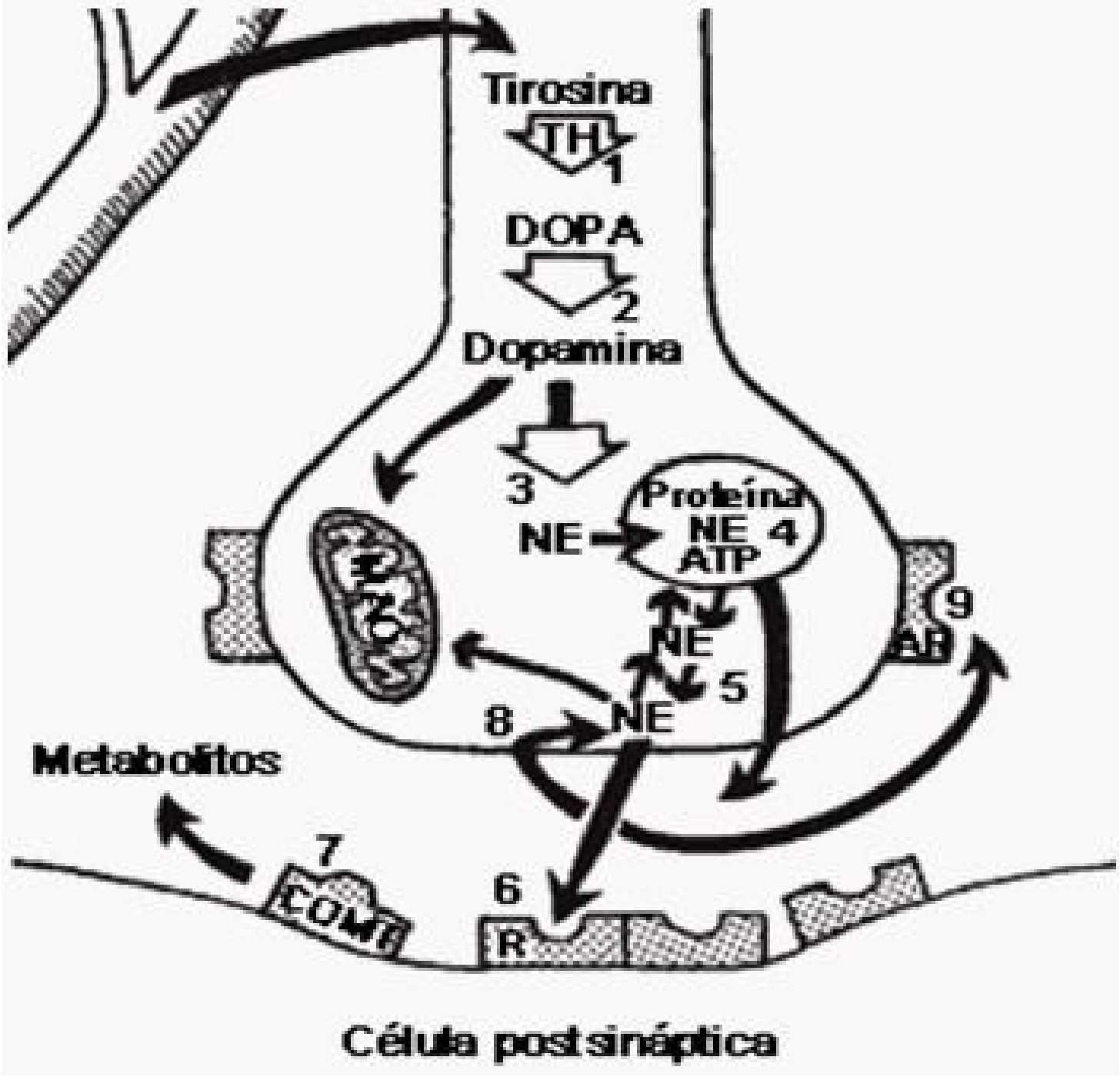
(AREA TEGMENTAL VENTRAL)

- TUBEROHIPOFISAL

(HIPOTALAMO N. ARQUEADO Y PARAVENTRICULAR AL LOBULO INTERMENDIO DE LA HIPOFISIS Y LA EMINENCIA MEDIA)

RETINA Y MEDULA ESPINAL


(A) Dopamine
Corpus callosum
Cerebral cortex
To striatum
Thalamus
Cerebellum
Substantia nigra and ventral tegmental area
Pons
Medulla
To spinal cord


Tirosina
TH
1
DOPA
2
Dopamina
3
Proteína
NE
ATP
4
NE
NE
5
NE
8
9
AR
Metabolitos
7
COMT
6
R
Célula postsináptica

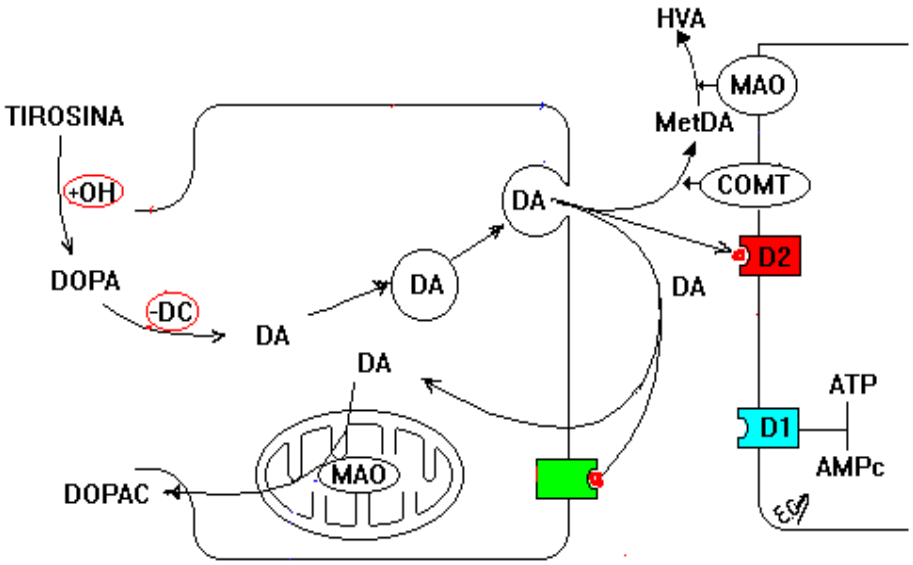
RE DOPAMINA

- RE ACOPLADOS A PROT G 7 DOMINIOS DE TRANSMEMBRANA Y UN TERCER BUCLE INTRACELULAR

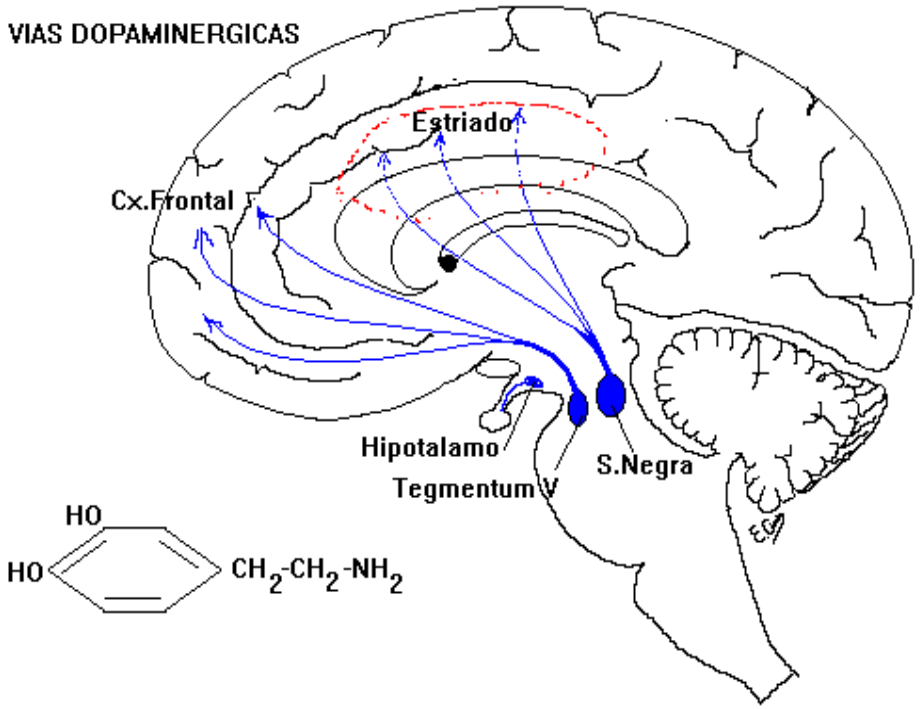
ACOPLADOS A ADENILATOCICLASA

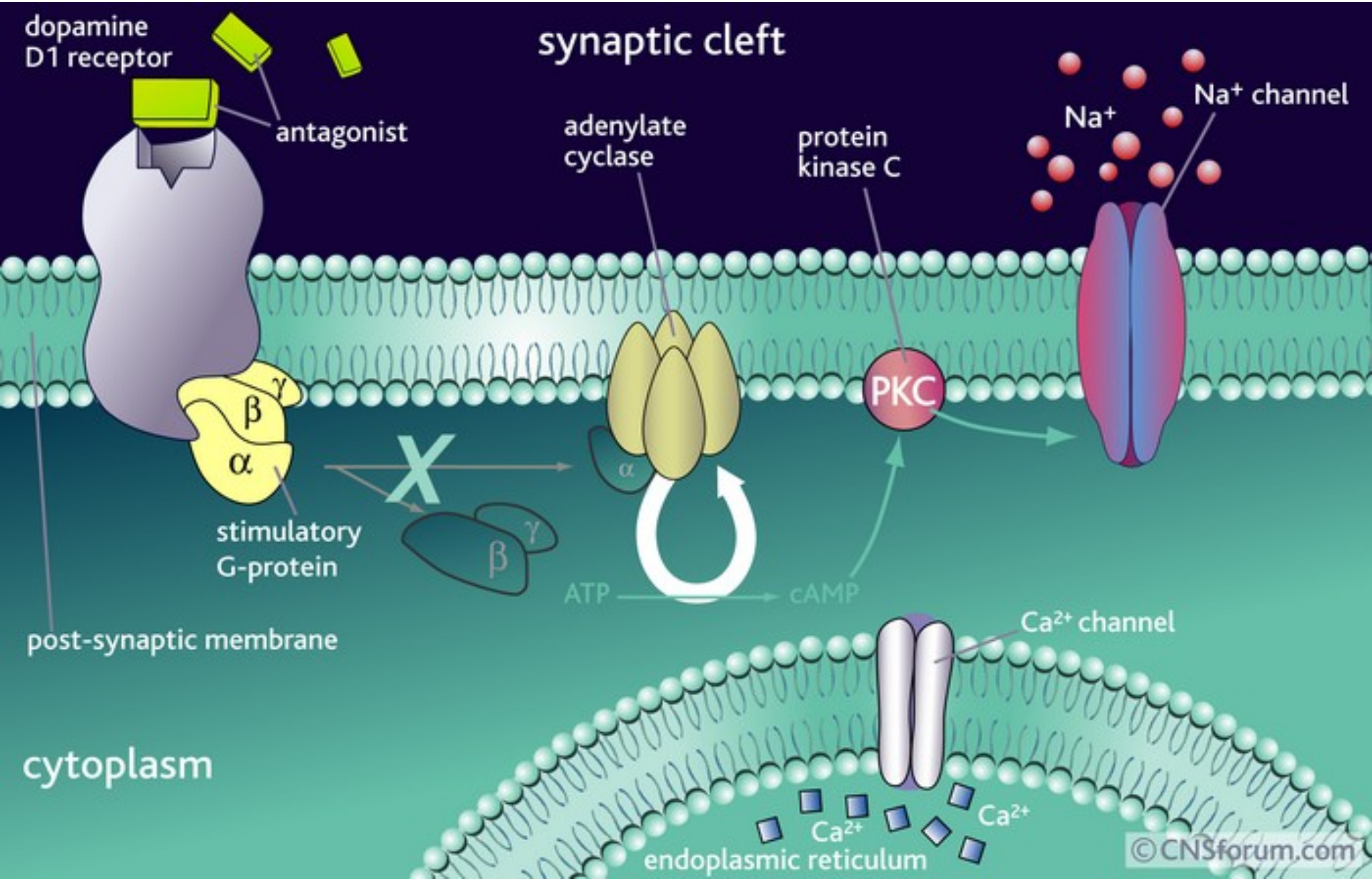
- D1 ESTRIADO DORSA Y ACUMBENS
- D2 ESTRIADO DORSAL ACUMBENS Y SUST NIGRA
- D3 N ACUMBENS Y CEREBEL
- D4 HIPOCAMPO, CEREBEL
- D5 HIPOCAMPO Y N PARAFASCICULAR

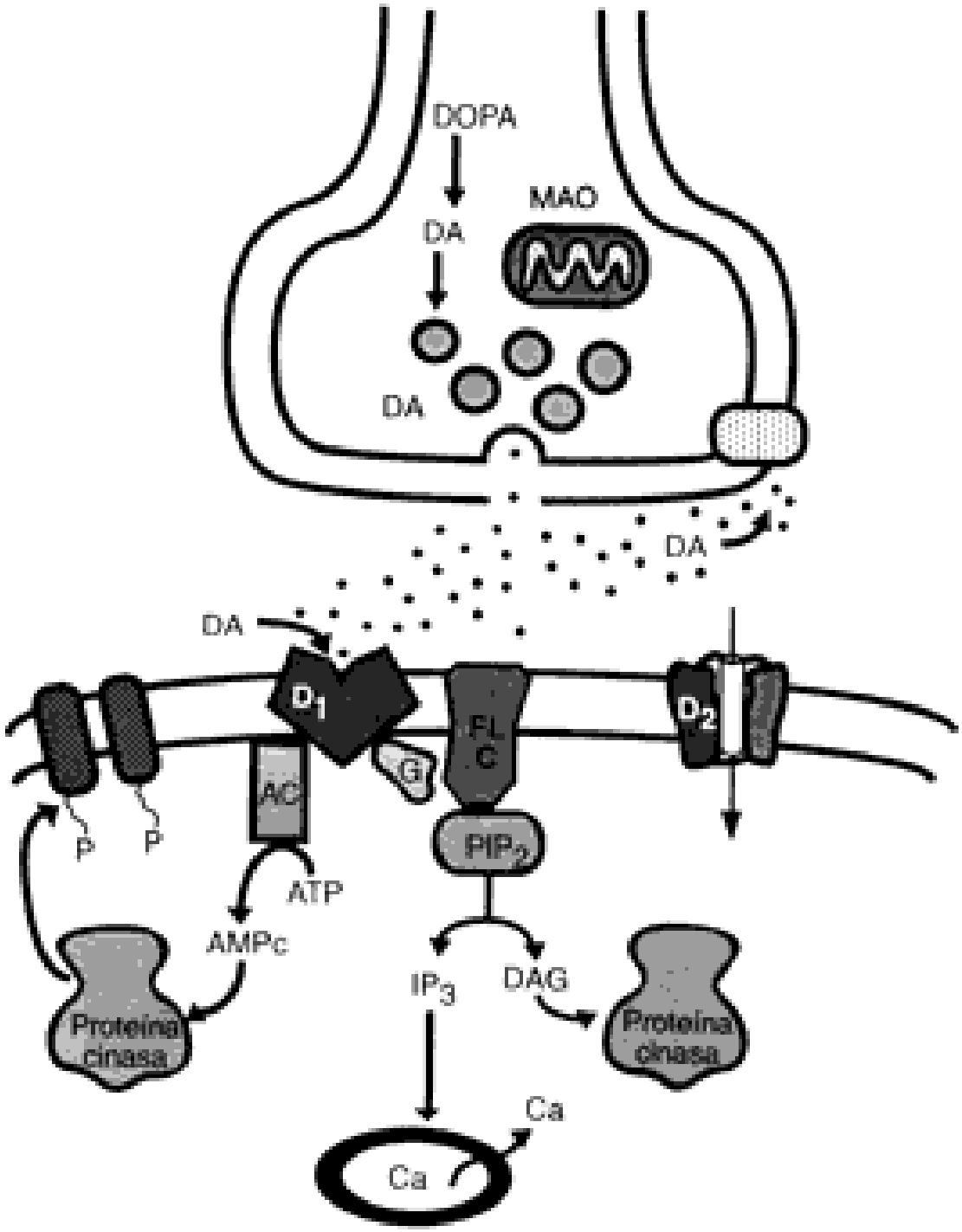
SINAPSIS DA



VIAS DOPAMINERGICAS




dopamine
D1 receptor
antagonist
synaptic cleft
adenylate
cyclase
protein
kinase C
Na+
Na+ channel
PKC
γ
β
α
stimulatory
G-protein
X
α
γ
β
ATP
cAMP
post-synaptic membrane
Ca2+ channel
cytoplasm
Ca2+
Ca2+
endoplasmic reticulum
©CNSforum.com


DOPA
DA
MAO
DA
DA
DA
D1
FL
C
G
AC
D2
P
P
ATP
AMPc
PIP2
IP3
DAG
Proteína cinasa
Proteína cinasa
Ca
Ca

Anfetaminas

DOPAMINA

EL TRANSPORTADOR DE MEMB. DE DOPAMINA ES BLANCO:

COCAINA, ANFETAMINA Y DERIVADOS ANALOGOS (METILENDIOXIMETANFETAMINAS NDMA)

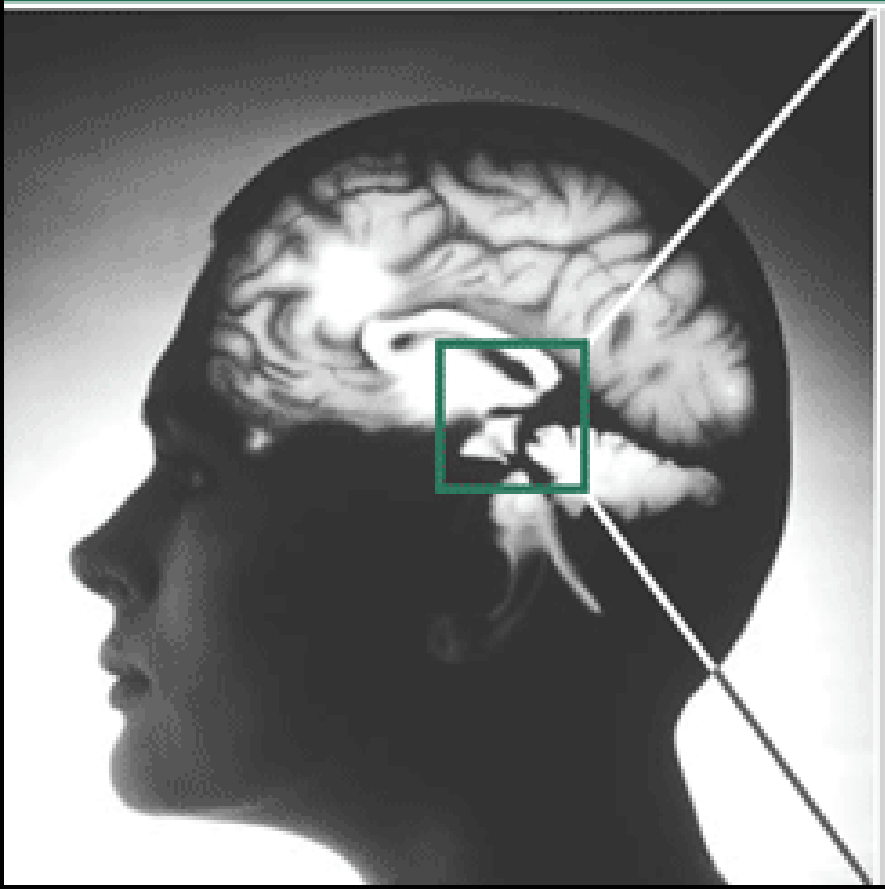
AUMENTA CONCENTRACION SINAPTICA DE DOPAMINA EN N. ACUMBENS O CORTEZA PREFRONTAL

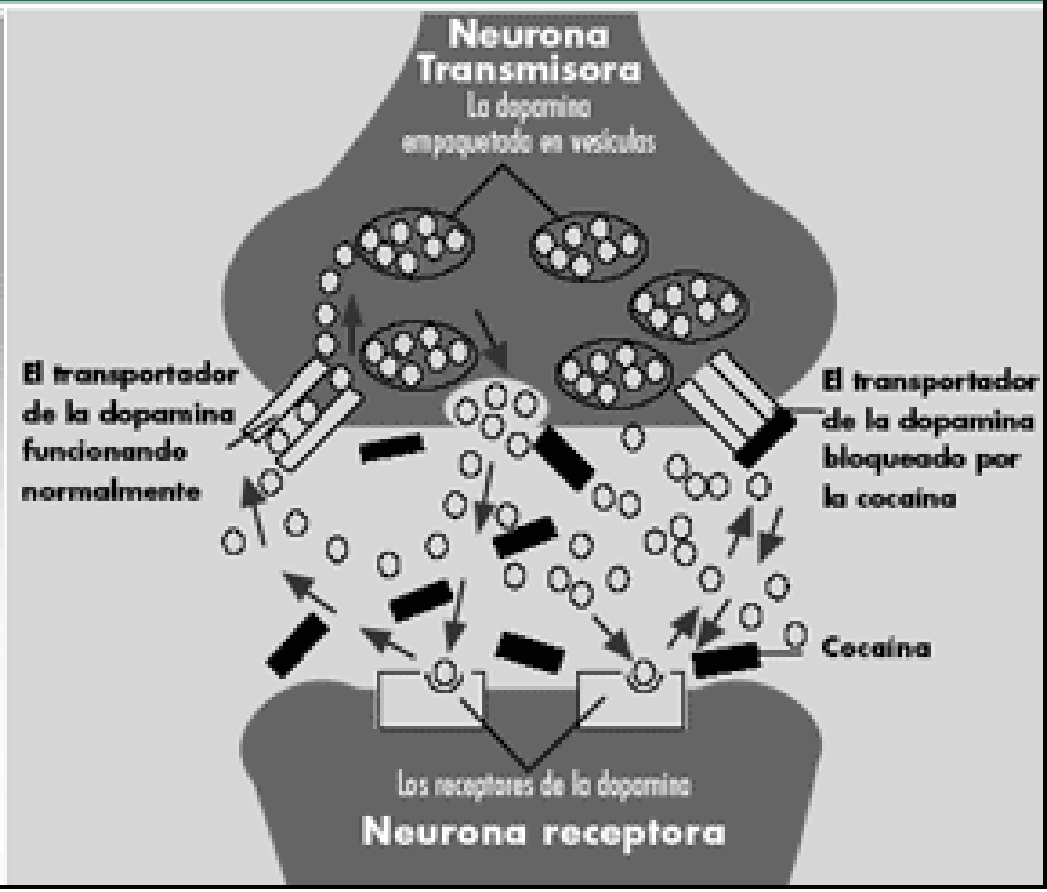
ESQUIZOFRENIA

- TTO ANTAGONISTAS DE RE DOPAMINERGICO D 2, HIPERACTIVIDAD DE VIA MESOLIMBICA

- ANTAGONISTAS GLUTAMATERGICOS NMDA COMO KETAMINA CURSAN CON CLINICA DE ESQUIZOFRENIA

Acción de la cocaína en el cerebro: En el proceso normal de comunicación, las neuronas liberan dopamina dentro de la sinapsis, donde se une a los receptores de dopamina en las neuronas adyacentes. Normalmente, una proteína especializada llamada la transportadora de dopamina recicla la dopamina de vuelta a la neurona transmisora. Cuando se ha consumido cocaína, ésta se adhiere a la transportadora de dopamina y bloquea el proceso normal de reciclaje, resultando en una acumulación de dopamina en la sinapsis, lo que contribuye a los efectos placenteros de la cocaína.





NORADRENALINA

- VIAS NORADRENERGICAS:

HAZ DORSA: LOCUS CERULEUS

APRENDIZAJE, RESPUESTA, ATENCION Y ANSIEDAD. LOCALIZADO EN NEOCORTEZA, HIPOCAMPO Y AMIGDALA

AUMENTO DE SIMPATICO ACTIVA LA LUCHA

HAZ VENTRAL: TRONCO DEL ENCEFALO E HIPOTALAMO

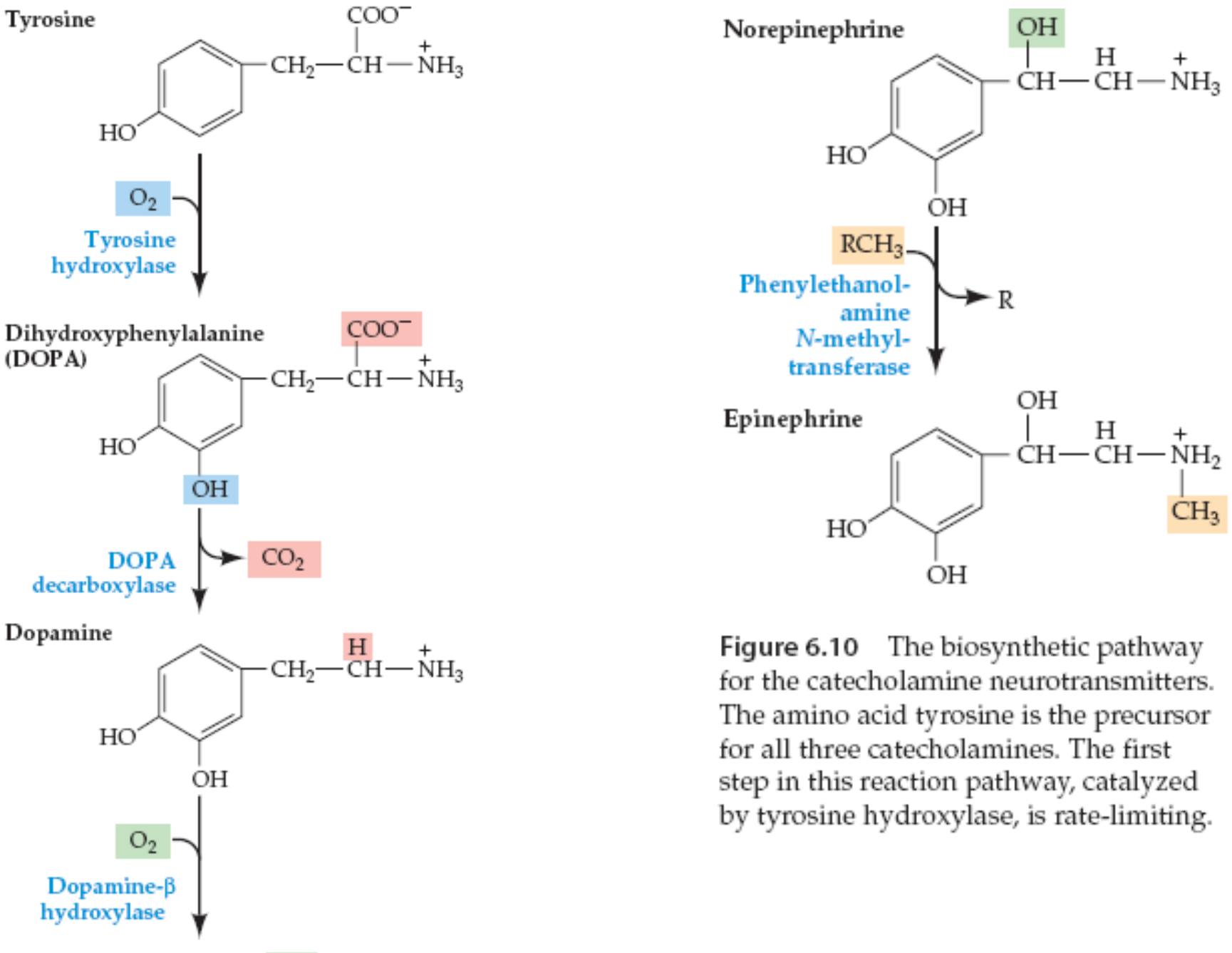
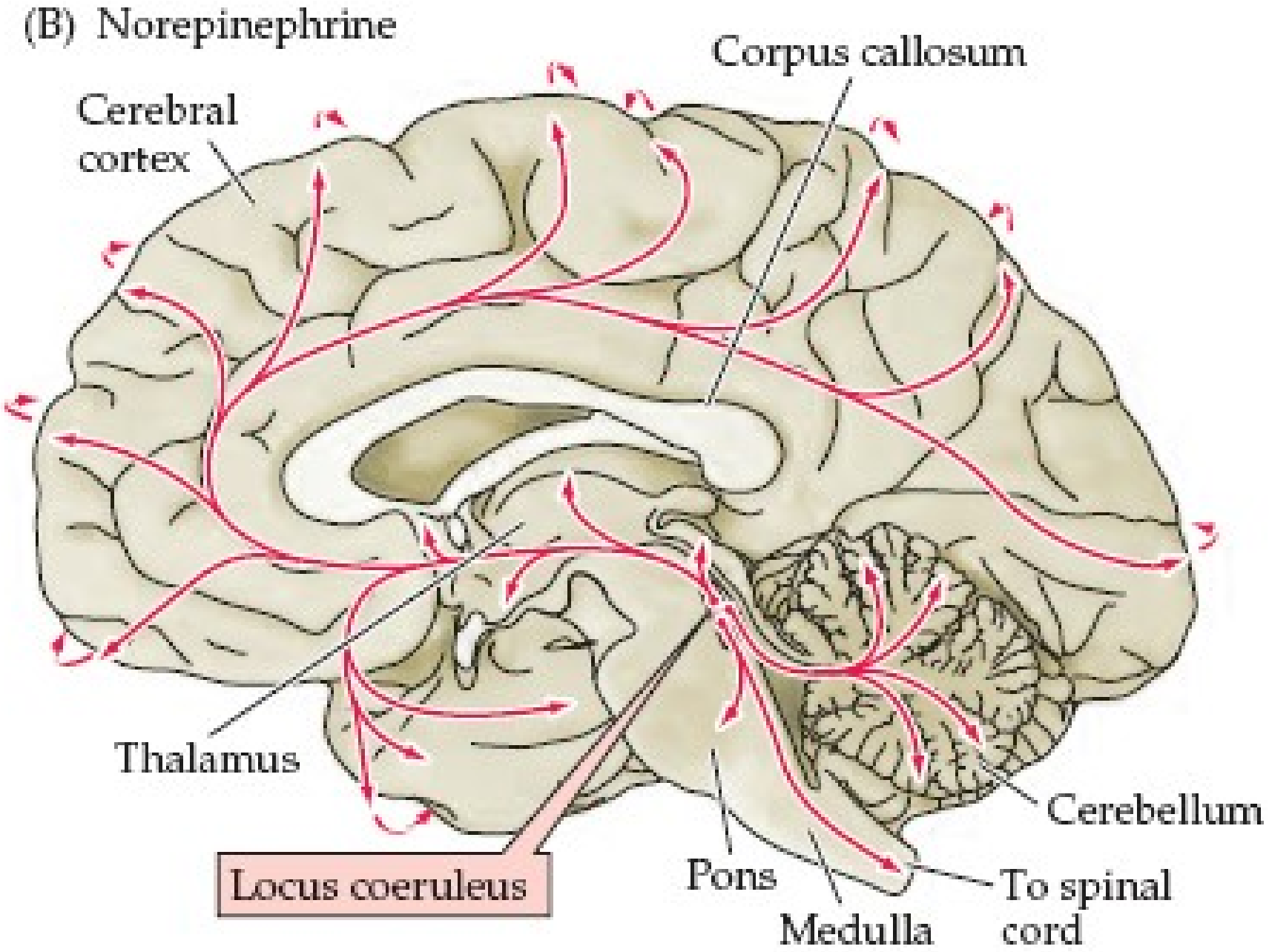
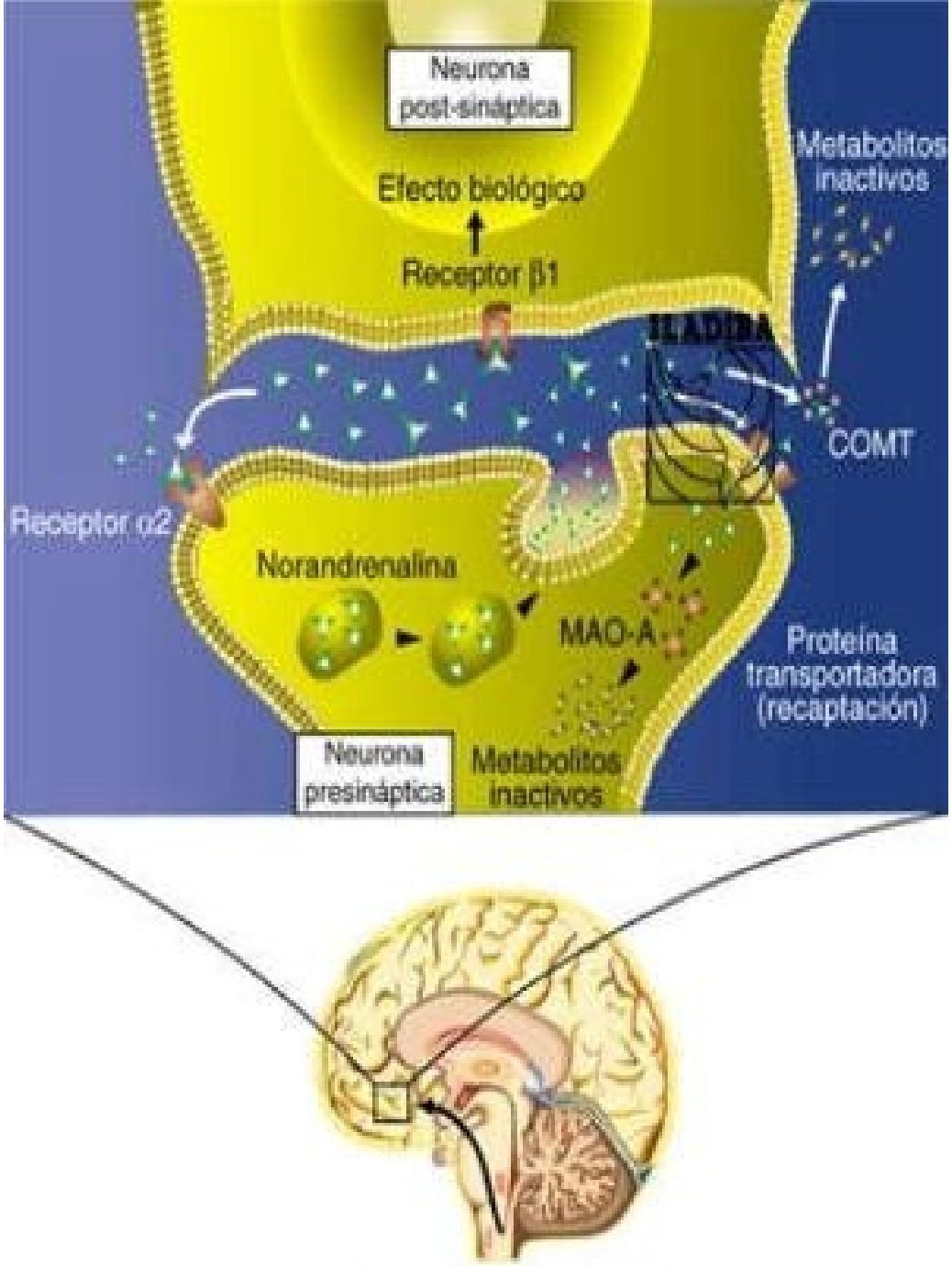


Figure 6.10 The biosynthetic pathway for the catecholamine neurotransmitters. The amino acid tyrosine is the precursor for all three catecholamines. The first step in this reaction pathway, catalyzed by tyrosine hydroxylase, is rate-limiting.


(B) Norepinephrine
Corpus callosum
Cerebral cortex
Thalamus
Locus coeruleus
Pons
Medulla
Cerebellum
To spinal cord

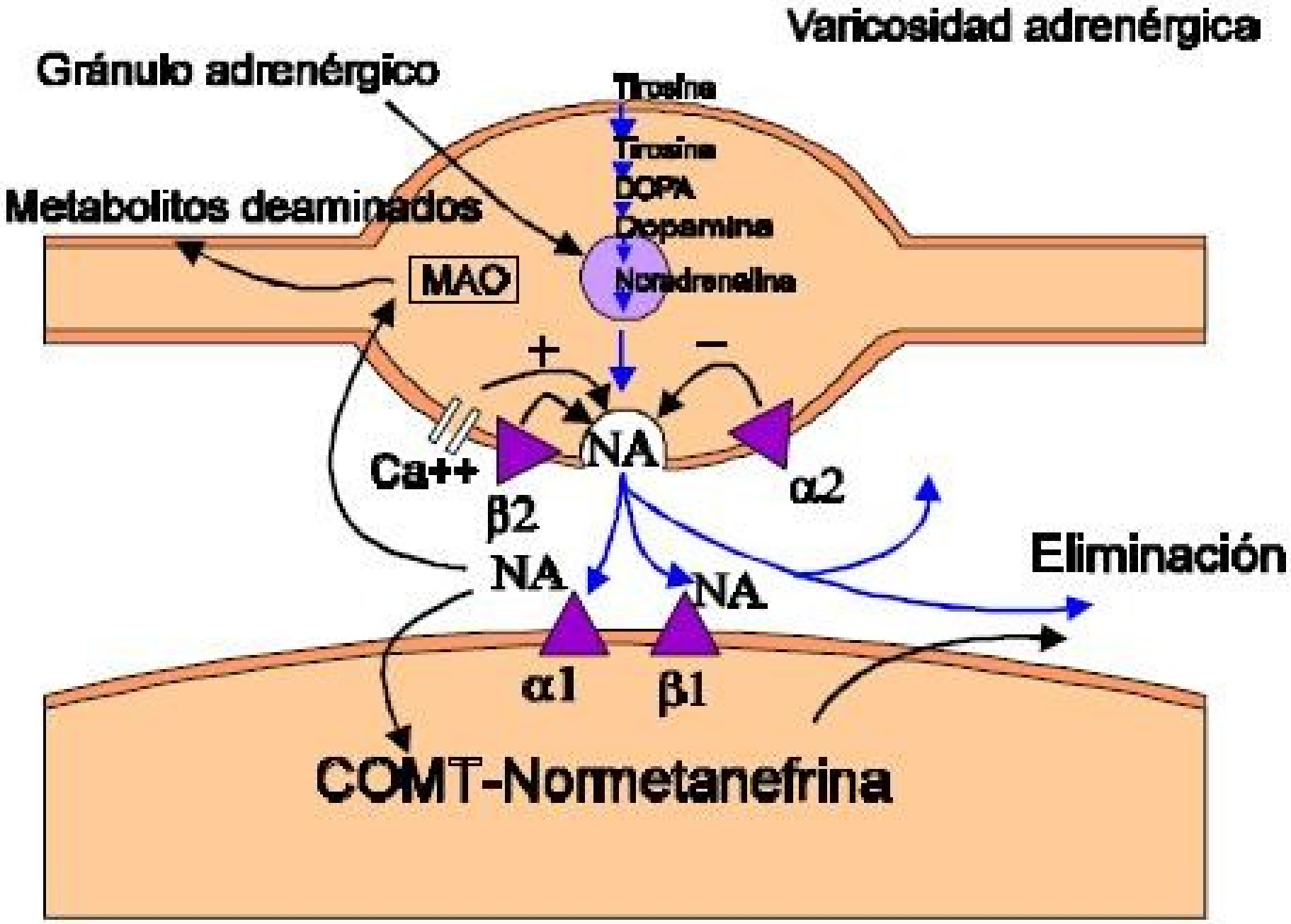
NORADRENALINA

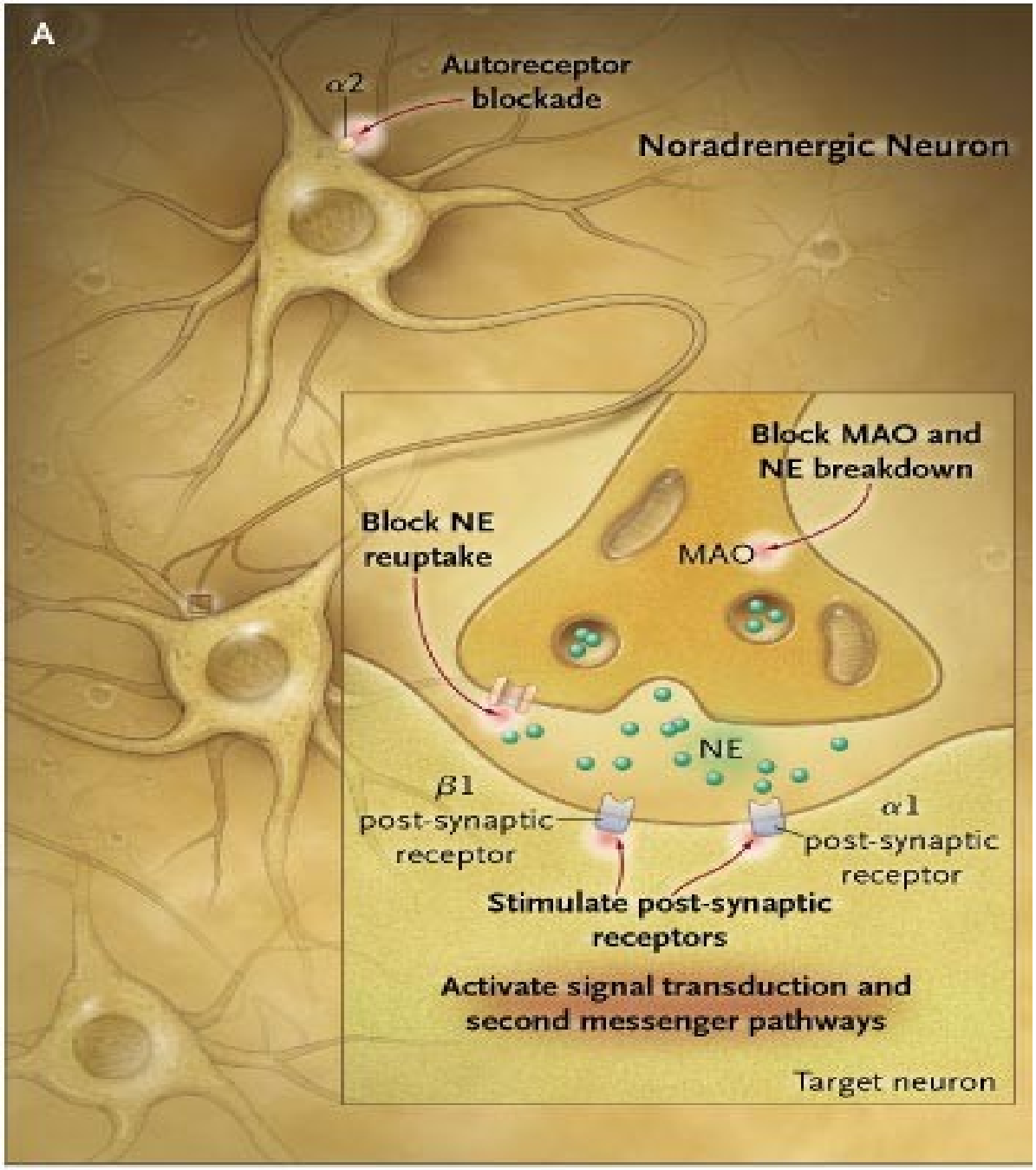
- NET :TRANSPORTADOR DE NORADRENALINA
- DEGRADADO POR: MAO Y COMT
- RE ACOPLADOS A PROT G
- RE BETA ADRENERGICO 1ER METABOTROPICO DESCRITO
- RE ALFA1: 4 RE ALFA2: 3, RE BETA: 3 TOTAL: 10
- RE ALFA 1: LENTA DESPOLARIZACION POR INH. CANALES DE K
- RE ALFA 2: LENTA HIPERPOLARIZACION POR ACTIVACION DEL CANAL DE K+
- RE BETA SON 3 ACOPLADOS + ADENILATOCICLASA



SINAPSIS NORADRENERGICA

NEUROTRANSMISIÓN ADRENÉRGICA




A
α2
Autoreceptor blockade
Noradrenergic Neuron
Block MAO and NE breakdown
Block NE reuptake
MAO
NE
β1 post-synaptic receptor
α1 post-synaptic receptor
Stimulate post-synaptic receptors
Activate signal transduction and second messenger pathways
Target neuron

ADRENALINA

- MENORES NIVELES
- SIST. TEGMENTAL LATERAL Y BULBO SE PROYECTAN A HIPOTALAMO Y TALAMO
- NO SE CONOCE LA FUNCION
- NO TIENE PROPIO TRANSPORTADOR USA EL NET
- ACTUA SOBRE RE ALFA Y BETA ADRENERGICOS

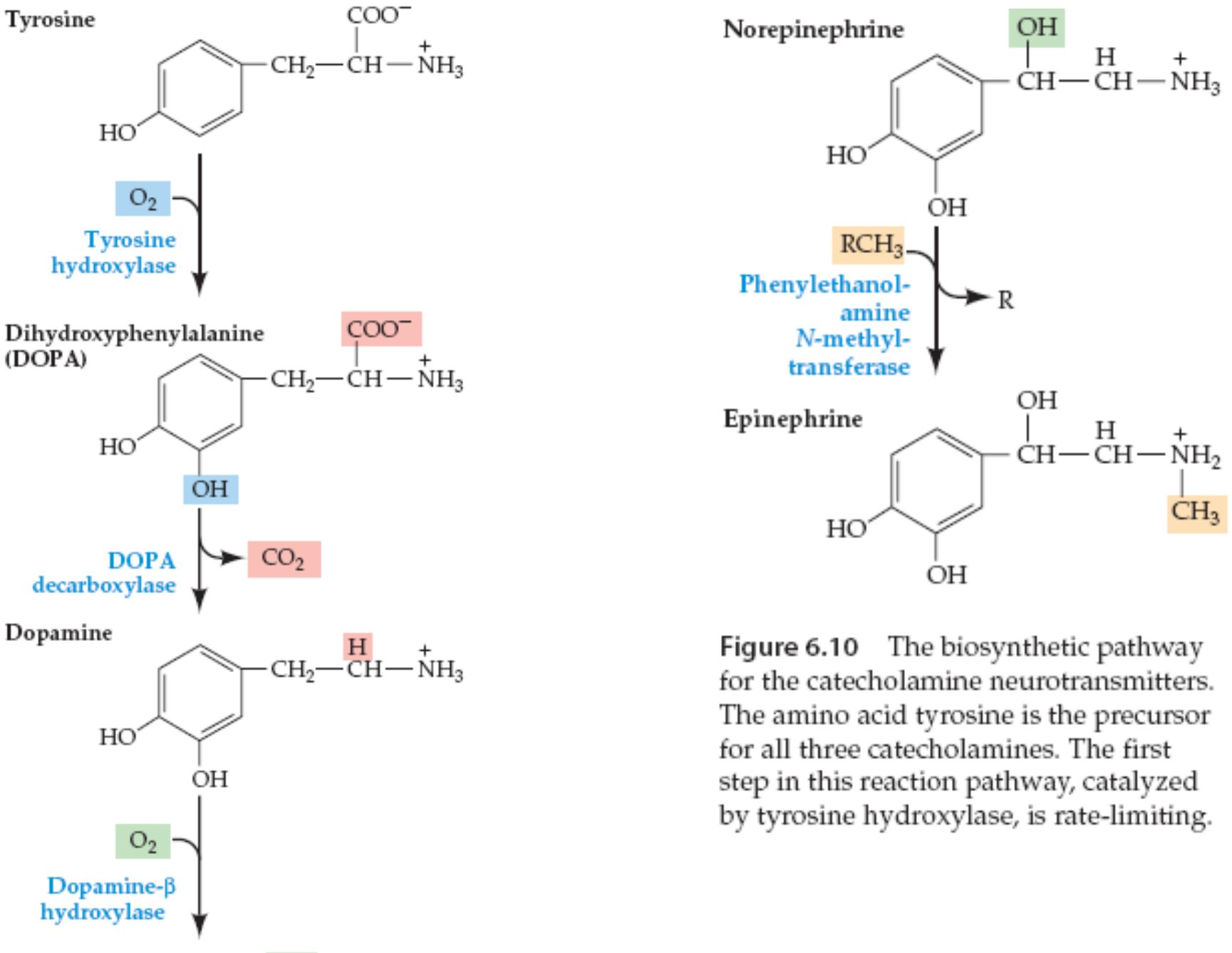
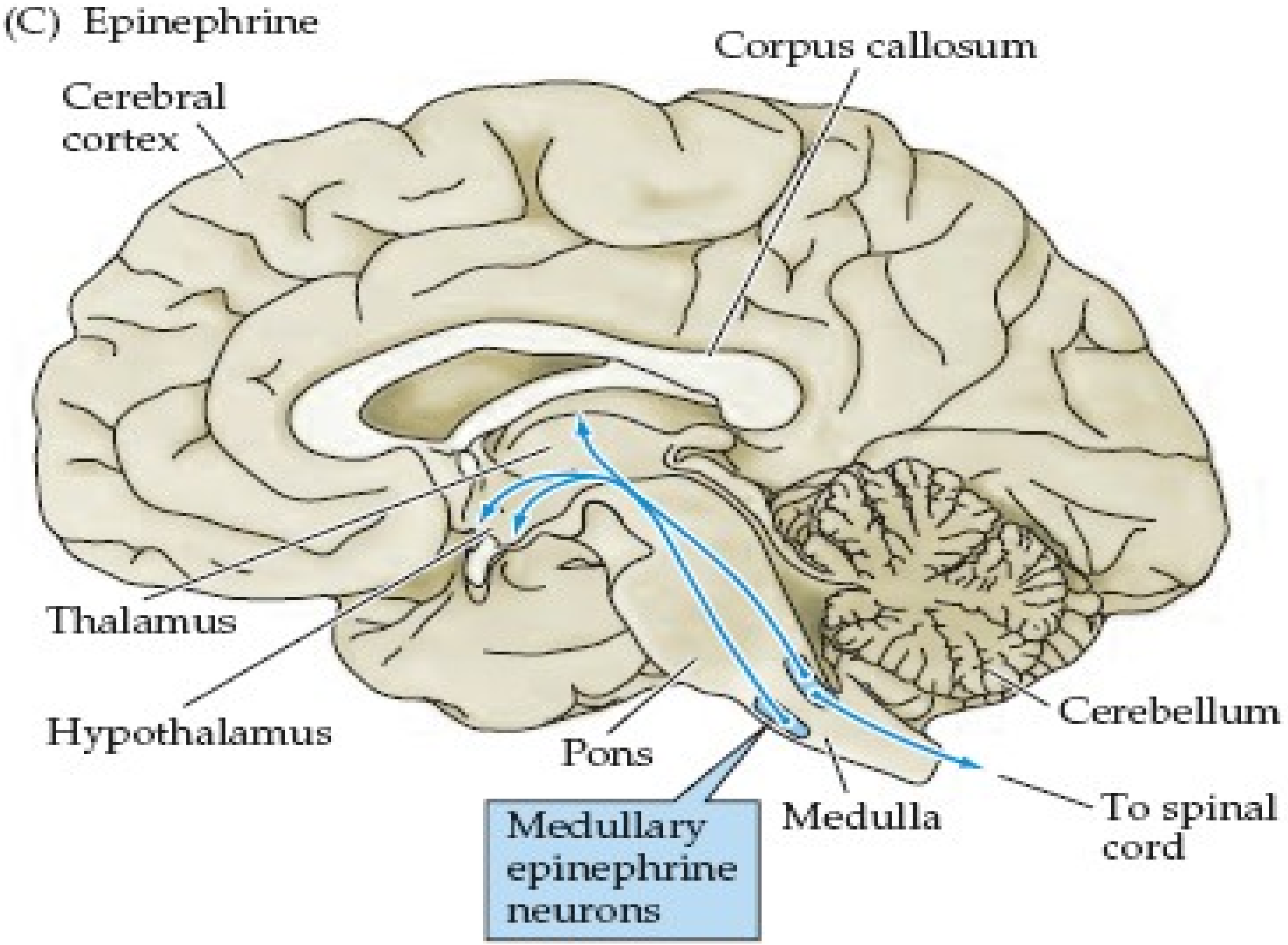
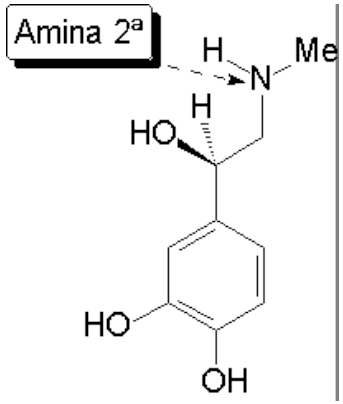
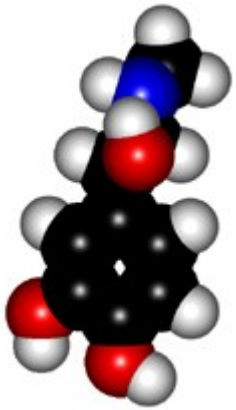
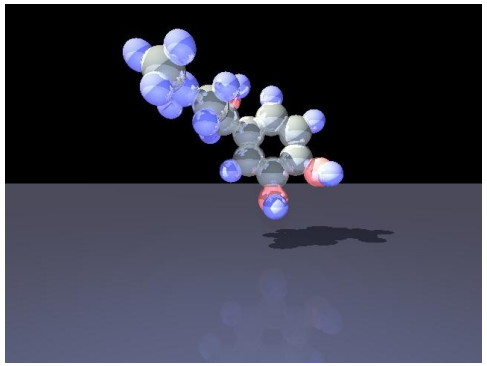


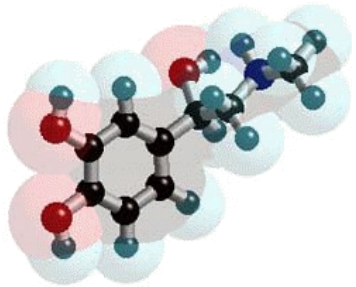
Figure 6.10 The biosynthetic pathway for the catecholamine neurotransmitters. The amino acid tyrosine is the precursor for all three catecholamines. The first step in this reaction pathway, catalyzed by tyrosine hydroxylase, is rate-limiting.


(C) Epinephrine
Corpus callosum
Cerebral cortex
Thalamus
Hypothalamus
Pons
Medullary epinephrine neurons
Medulla
Cerebellum
To spinal cord

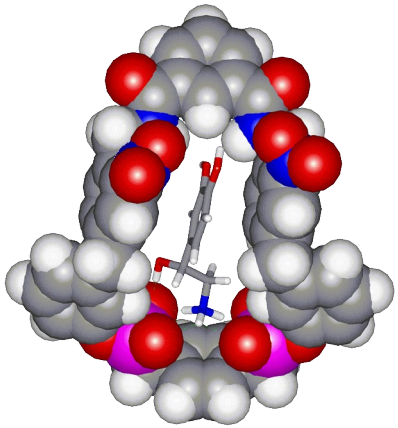




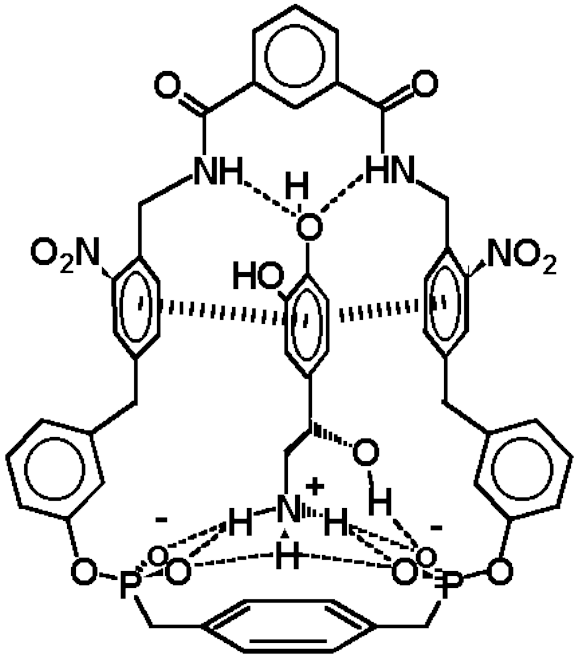


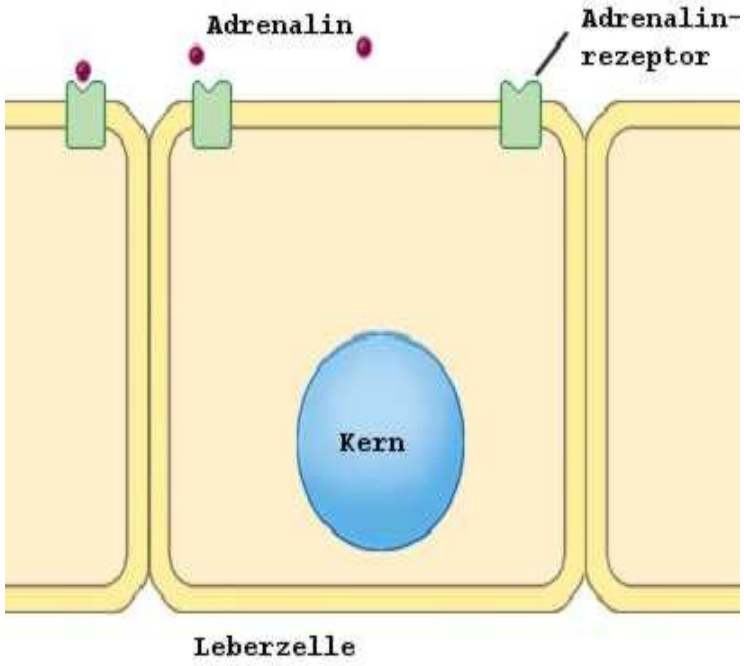


Adrenalina y noradrenalina



Receptores de las catecolaminas

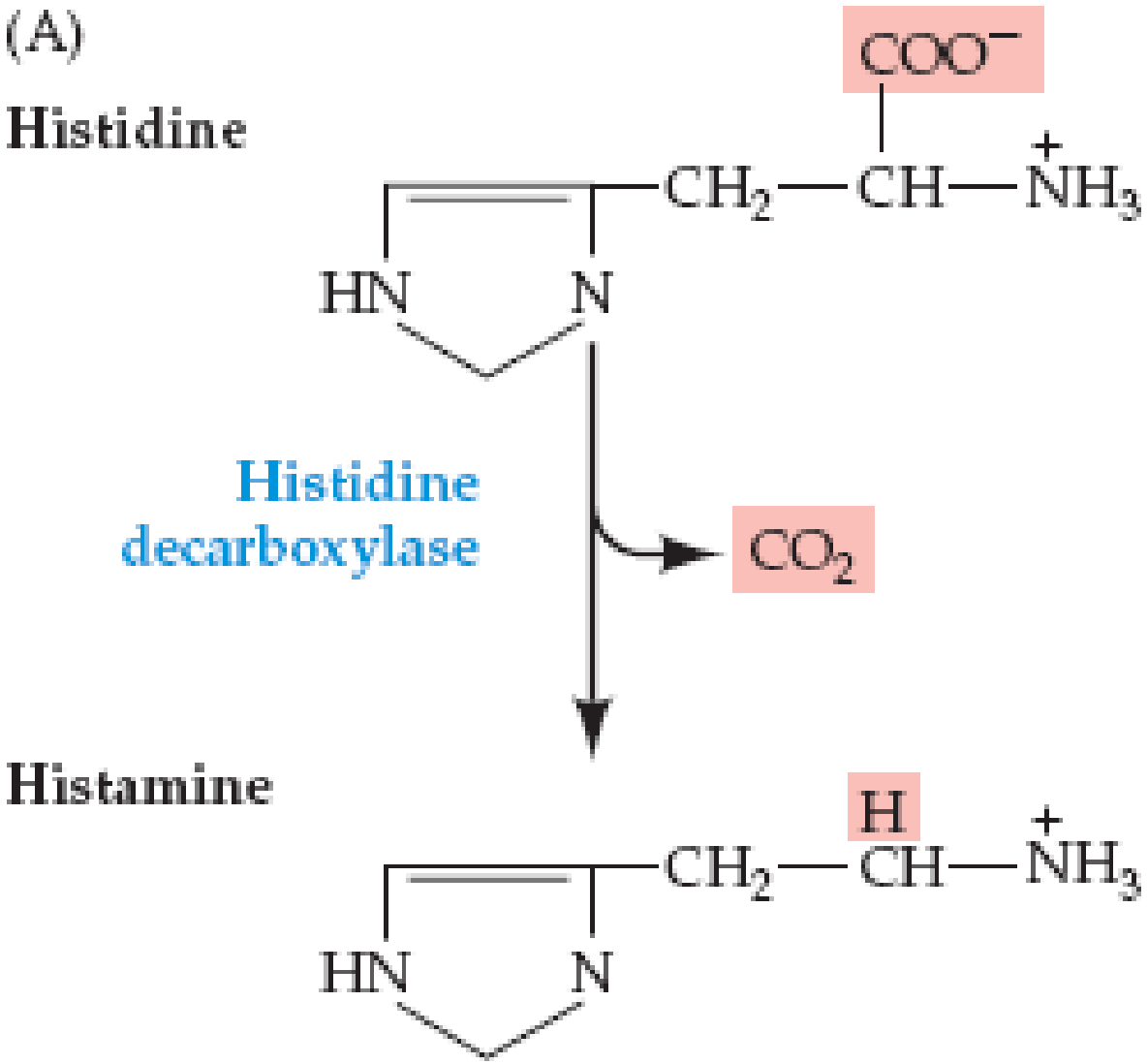


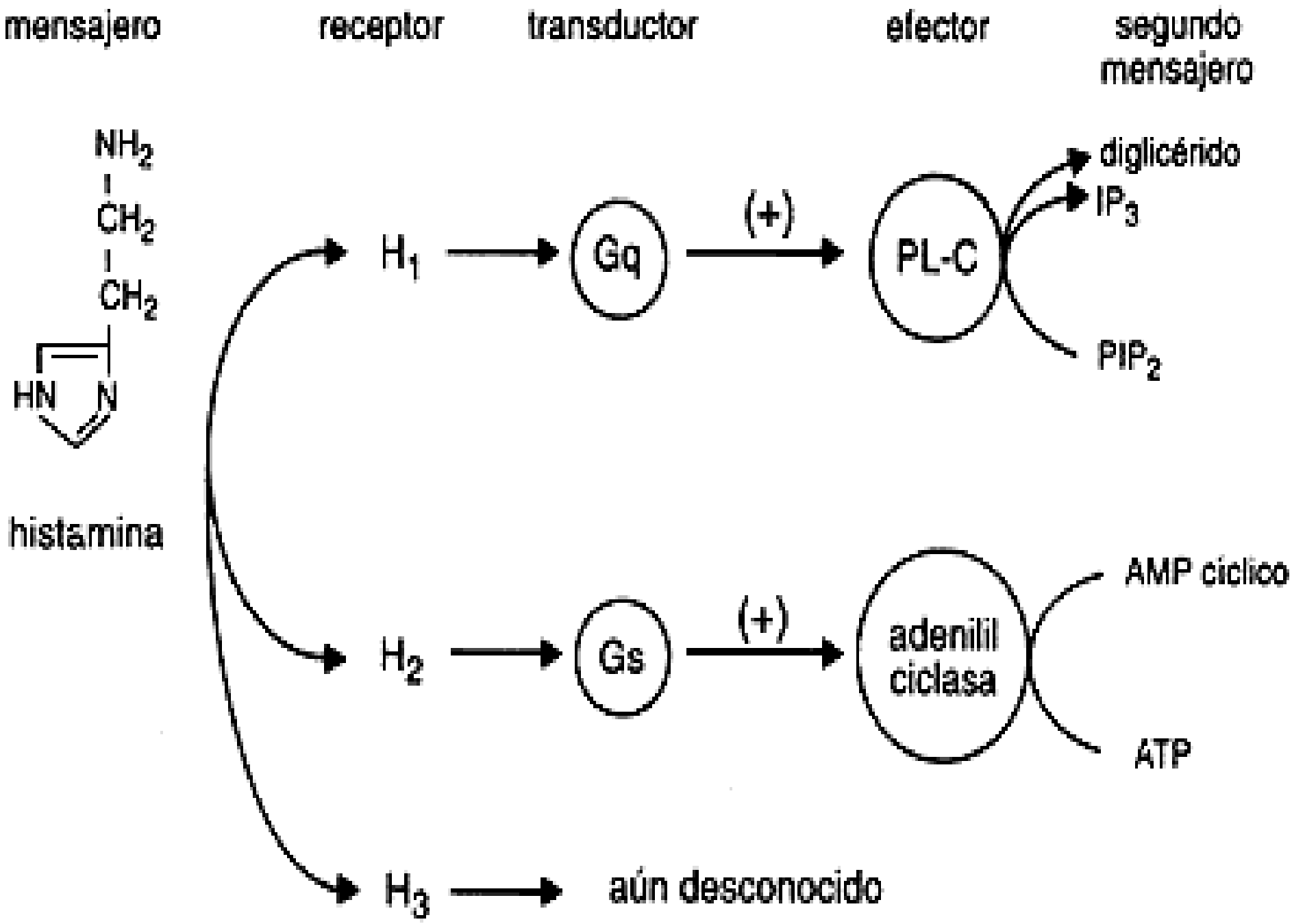


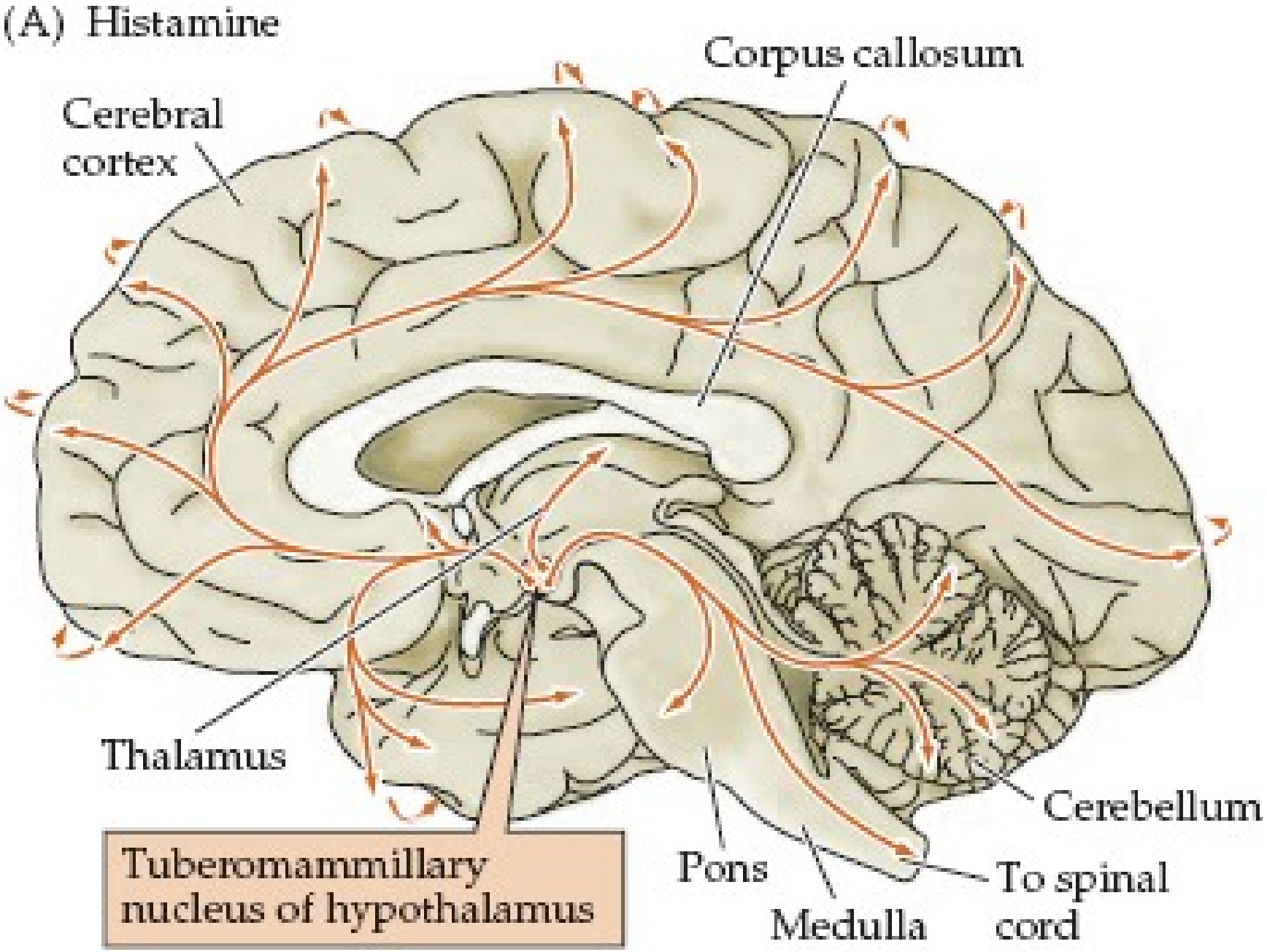
HISTAMINA

- SE ENCUENTRA EN N. HIPOTALAMO Y DE ALLI A ENCEFALO Y MEDULA ESP.
- MEDIAN DESPERTAR Y ATENCION
- REACTIVIDAD DEL SIST. VESTIBULAR
- REACCONES ALERGICAS LIBERAN HISTAMINA DESDE EL MASTOCITO
- SINTESIS A PARTIR DE LA HISTIDINA Y SE TRANSPORTA POR VMAT
- DEGRADADA POR HISTAMINA METIL TRANFERASA Y MAO

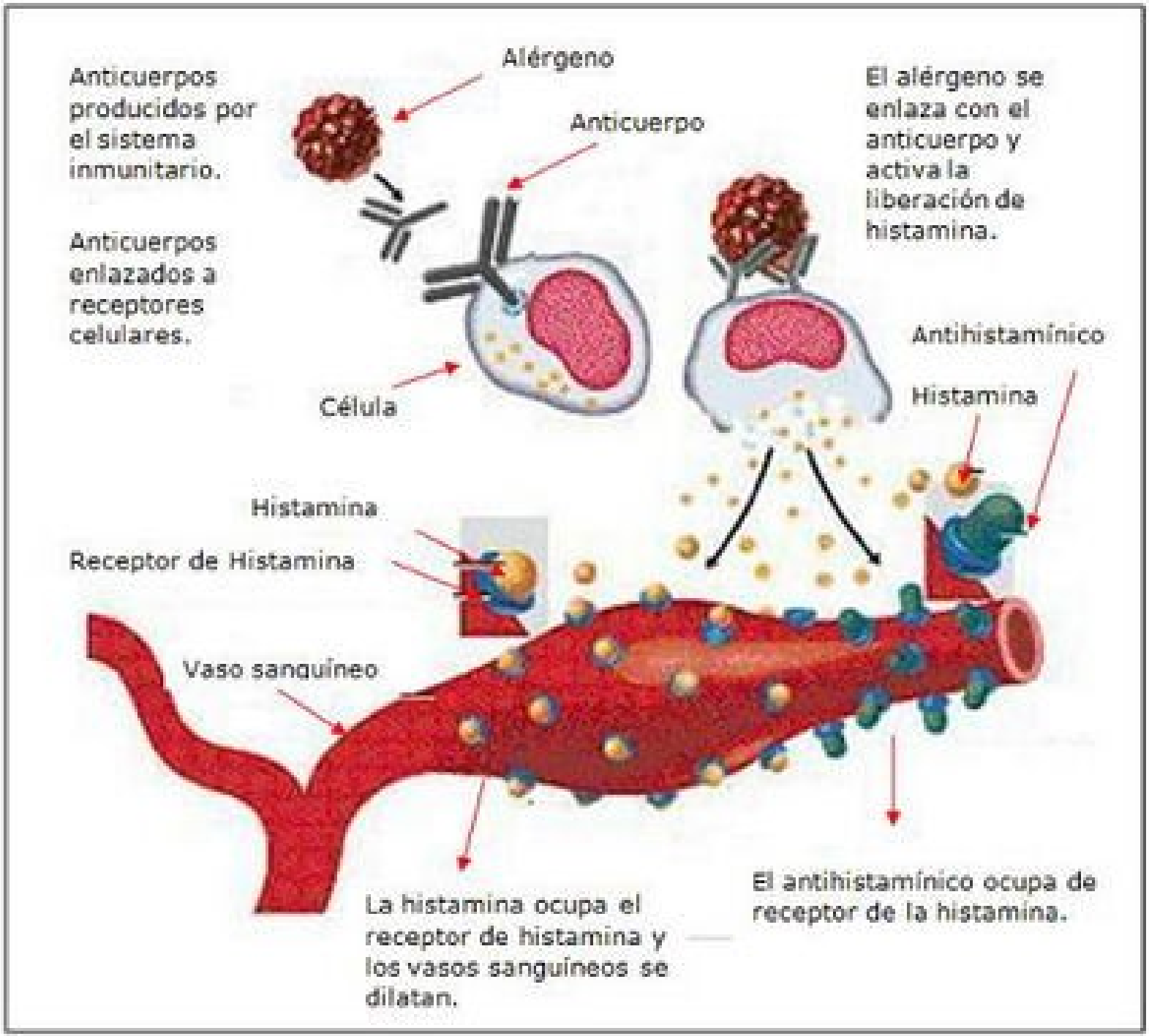
(A)


Histidine
COO⁻
CH₂
CH
NH₃
HN
N
Histidine decarboxylase
CO₂
Histamine
H
CH₂
CH
NH₃
HN
N


mensajero
receptor
transductor
efector
segundo mensajero
NH2
CH2
CH2
HN
N
histamina
H1
Gq
(+)
PL-C
diglicérido
IP3
PIP2
H2
Gs
(+)
adenilil ciclasa
AMP cíclico
ATP
H3
aún desconocido


(A) Histamine
Corpus callosum
Cerebral cortex
Thalamus
Tuberomammillary nucleus of hypothalamus
Pons
Medulla
Cerebellum
To spinal cord

Los mastocitos liberan histaminas cuando se encuentran con un alergeno
A.D.A.M.

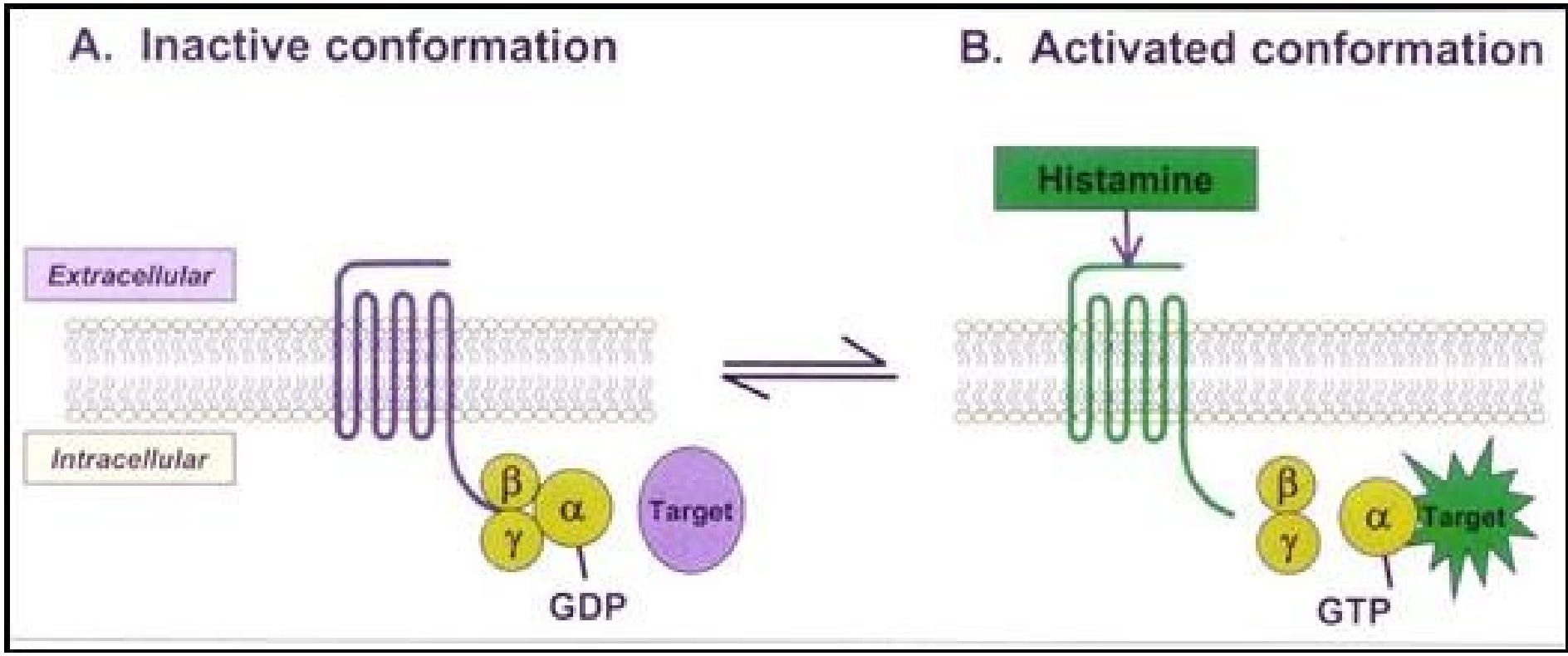

Anticuerpos producidos por el sistema inmunitario.
Alérgeno
Anticuerpo
El alérgeno se enlaza con el anticuerpo y activa la liberación de histamina.
Anticuerpos enlazados a receptores celulares.
Célula
Antihistamínico
Histamina
Histamina
Receptor de Histamina
Vaso sanguíneo
La histamina ocupa el receptor de histamina y los vasos sanguíneos se dilatan.
El antihistamínico ocupa de receptor de la histamina.

EN EL ASMA LOS RECEPTORES H1 PUEDEN OCASIONAR:
CONTRACCIÓN DEL MÚSCULO LISO BRONQUIAL
Y ESTIMULAR LA PRODUCCIÓN DE MOCO EN LAS GLÁNDULAS.
EN LA PIEL PRODUCEN CONTRACCIÓN
DE LAS CÉLULAS ENDOTELIALES DE LAS VÉNULAS POST CAPILARES CAUSANDO
LA APARICIÓN DE RONCHAS Y ESTIMULAN A LAS FIBRAS C PARA OCASIONAR PRURITO.

Receptores de HISTAMINA

(SUBTIPOS)

Sublipo Receptor	Distribucion	Mecanismo Post-Receptor
H1	Musculo liso, endo-telio y cerebro.	↑ IP3, DAG
H2	Mucosa gastrica, musculo cardiaco, mastocitos y cerebro	↑ cAMP
H3	Presinapticos: Ce-rebro, plexo miente-rico y otras neuronas	Proteina G


A. Inactive conformation
B. Activated conformation
Histamine
Extracellular
Intracellular
β
γ
α
Target
GDP
β
γ
α
Target
GTP

ANTIHISTAMINICOS

- H1: ENFERMEDAD DEL MOVIMIENTO
- H2: CONTROL DE SECRECION DE ACIDO GASTRICO

SEROTONINA
5 HIDROXITRIPTAMINA 5 HT

- AUMENTA TONO VASCULAR
- LA MAYOR PARTE SE ENCUENTRA FUERA DEL CEREBRO, EN CEL, ENTEROCROMAFINES DEL INTESTINO, MASTOCITOS Y PLAQUETAS.
- 1-2 % EN SNC: N. RAFE DEL PUENTE Y TRONCO DEL ENCEFALO SUPERIOR PROYECCIONES AL ENCEFALO ANTERIOR.
- REGULAN SUEÑO Y VIGILIA

SEROTONINA

- PROYECCIONES:

NUCLEO DORSAL DEL RAFE: AREAS MOTORAS (SUST. NIGRA, ESTRIADO)

NUCLEO MEDIAL DEL RAFE: HIPOCAMPO Y ZONAS LIMBICAS.

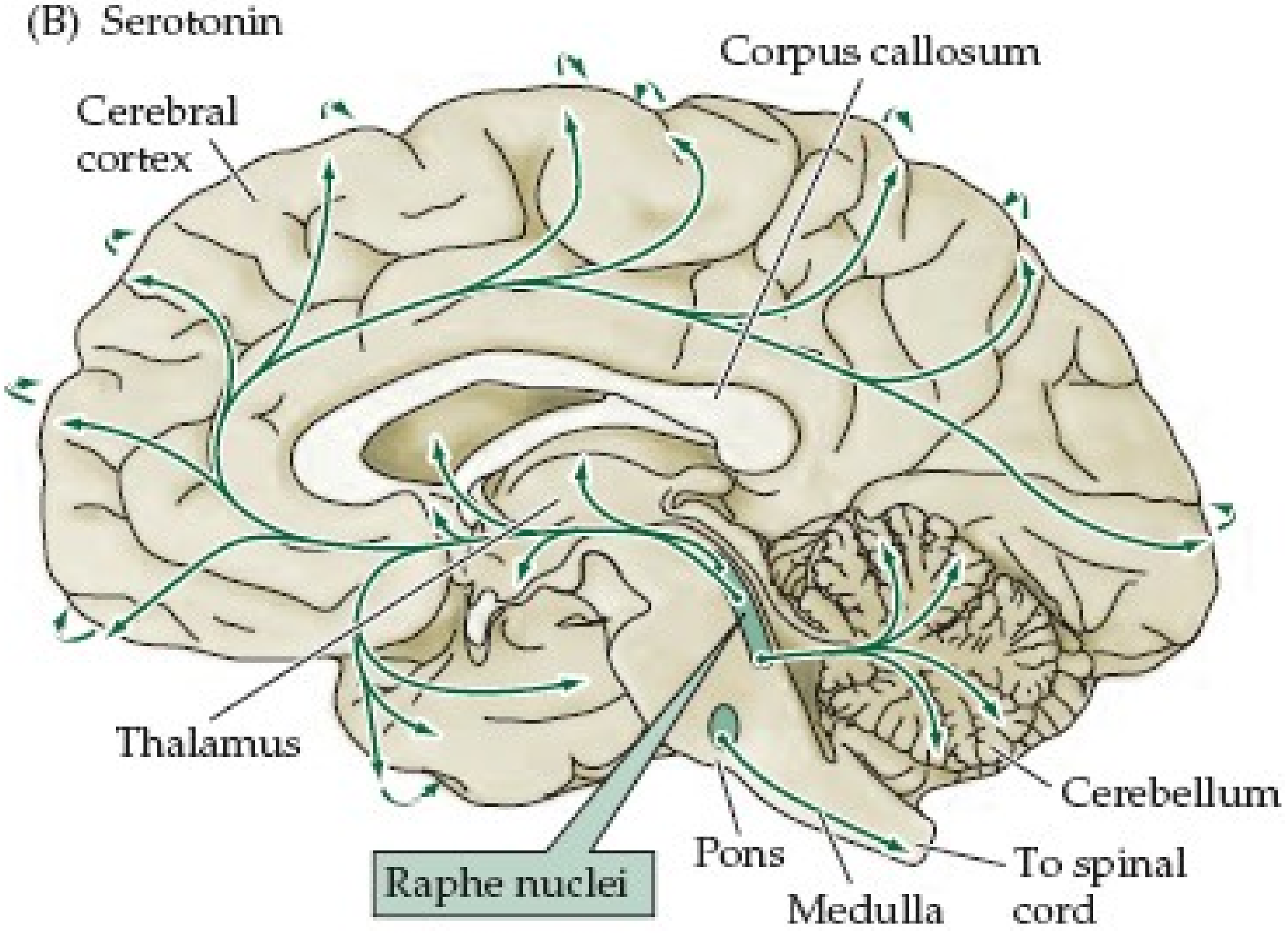
SEROTONINA

- SINTETIZADO APARTIR DEL TRIPTOFANO
- VMAT TRANSPORTA HACIA LAS VESICULAS
- TRANSPORTADOR RETROGRADO ESPECIFICO SERT
- VIA CATABOLICA MAO

RE SEROTONINA

- METABOTROPICOS
- PARTICIPAN EN LAS EMOCIONES, RITMO CIRCADIANO, CONDUCTA MOTORA Y ESTADO DE ALERTA MENTAL.
- MEDIA SACIEDAD Y CONSUMO DE ALIMENTO
- RE 5 HT3 SON IONOTROPICOSRESPUESTAS POSTSINAPTICAS EXCITADORAS

EJ: ONDANSETRON


(B) Serotonin
Corpus callosum
Cerebral cortex
Thalamus
Cerebellum
Raphe nuclei
Pons
Medulla
To spinal cord

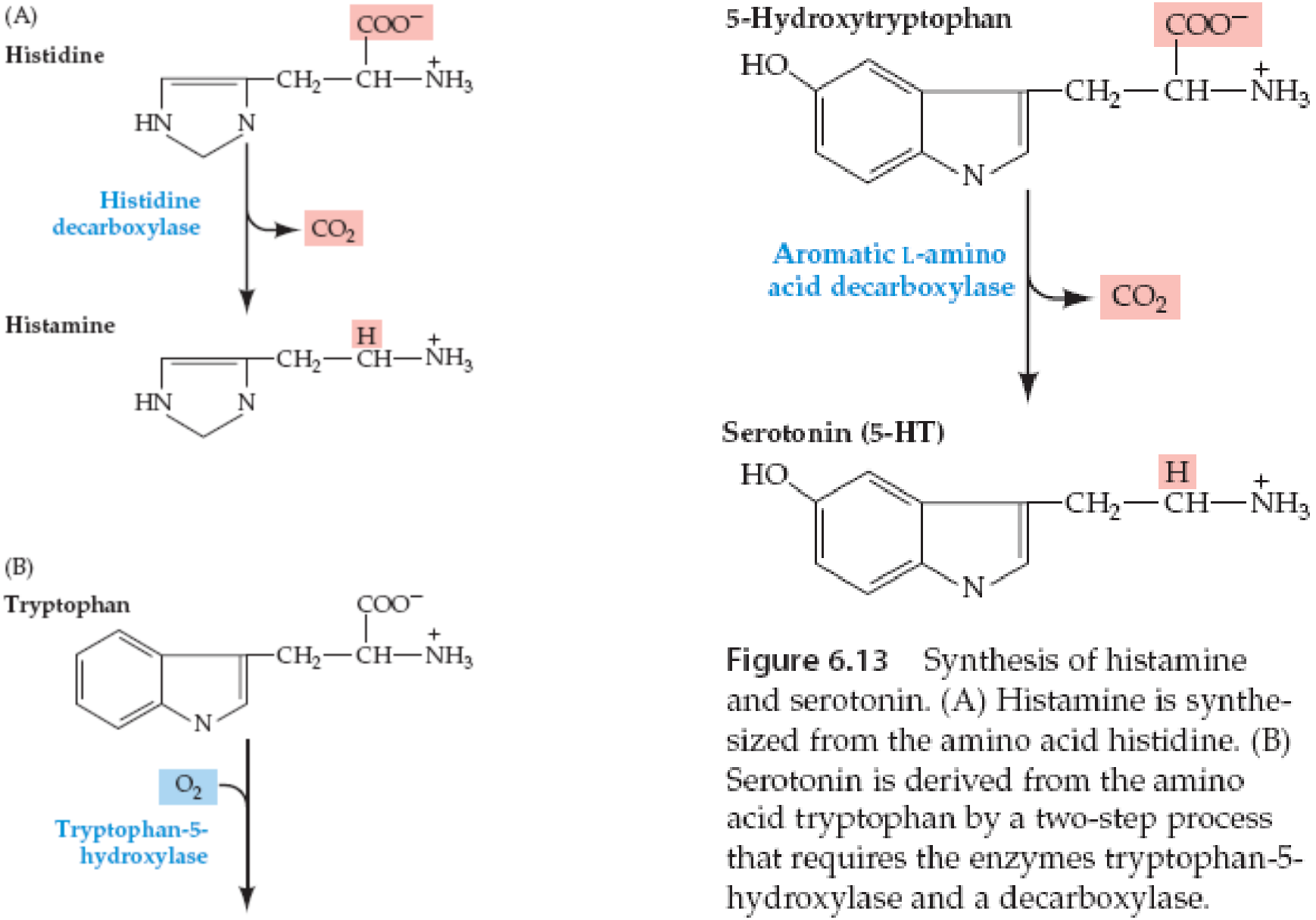
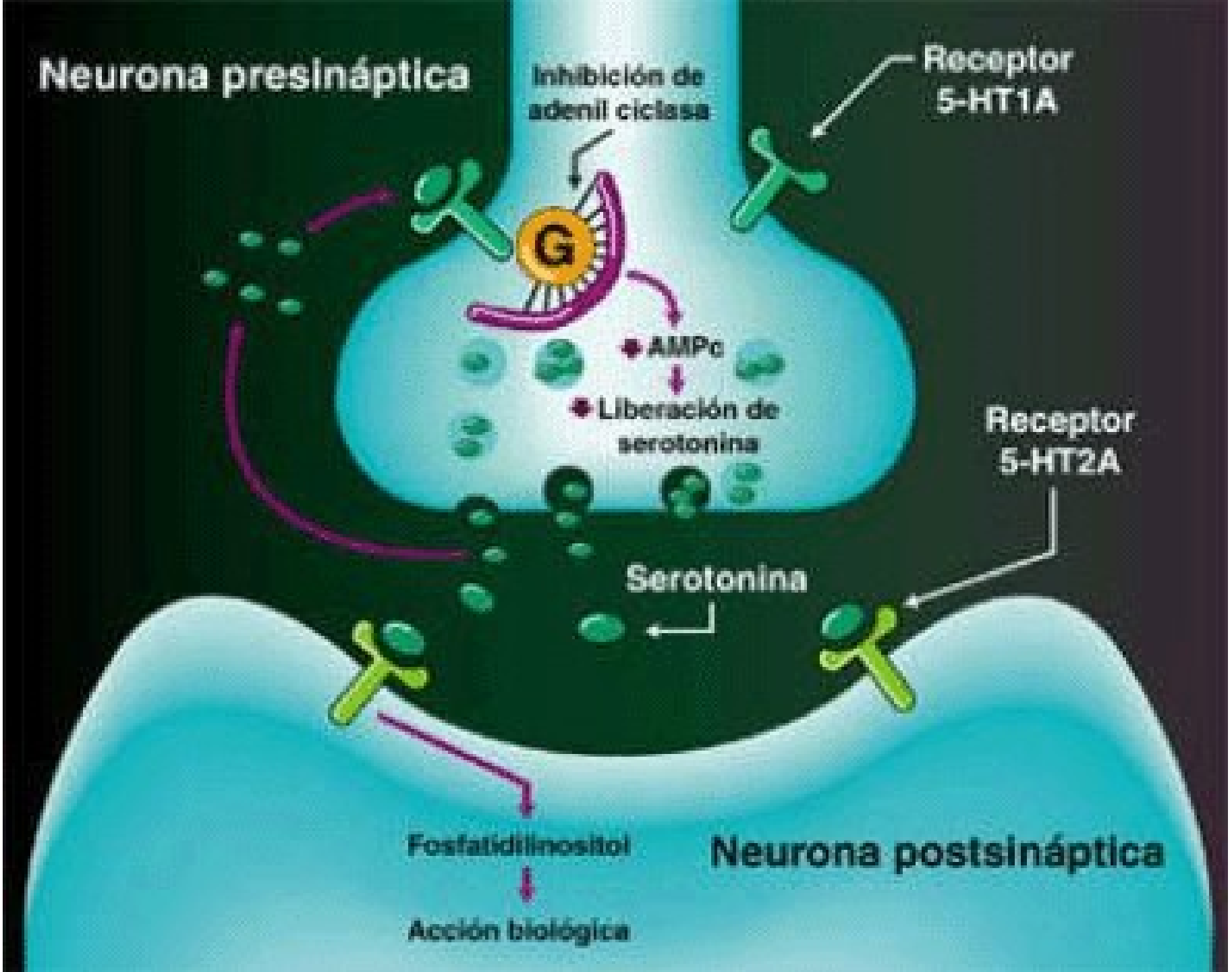
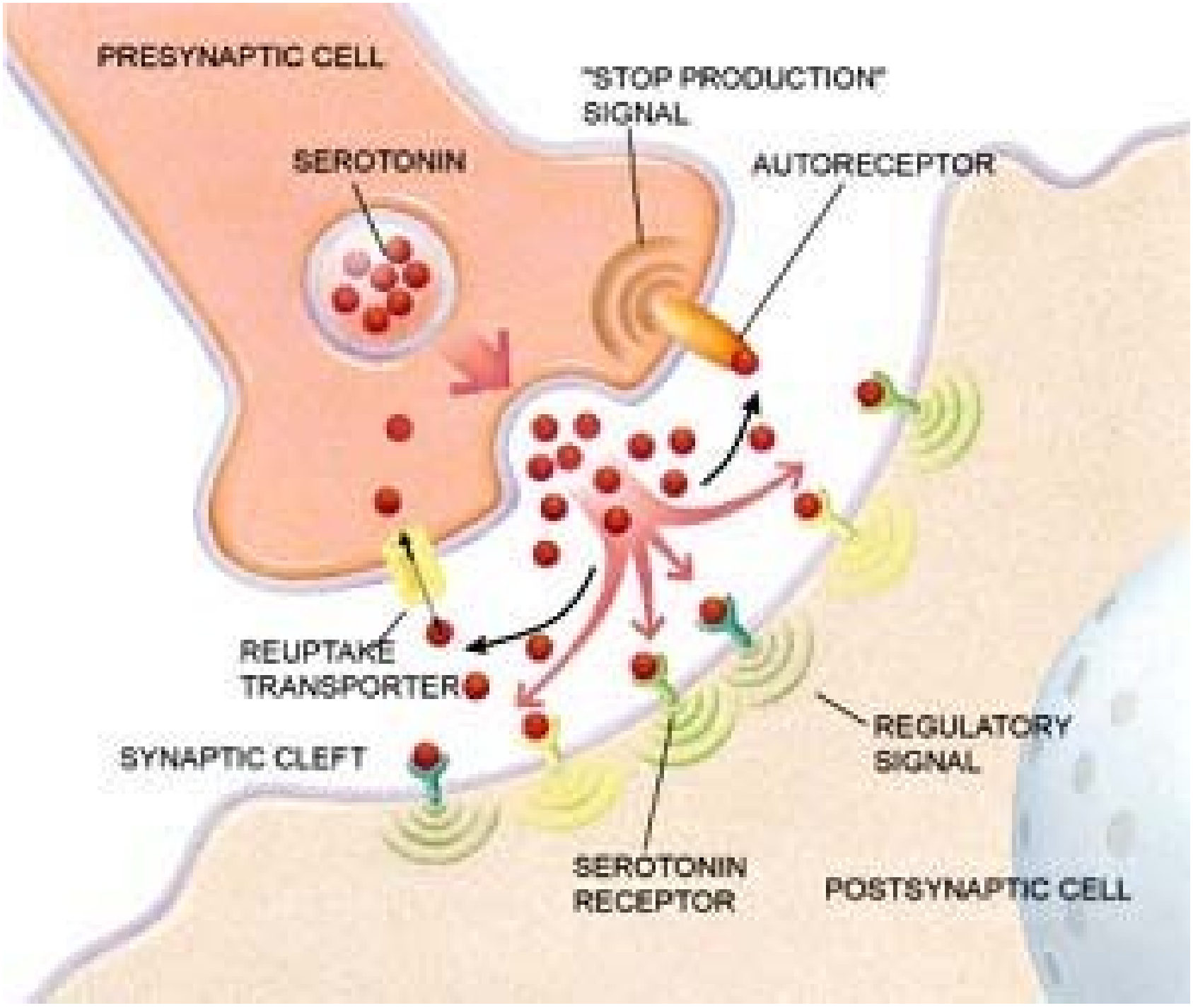
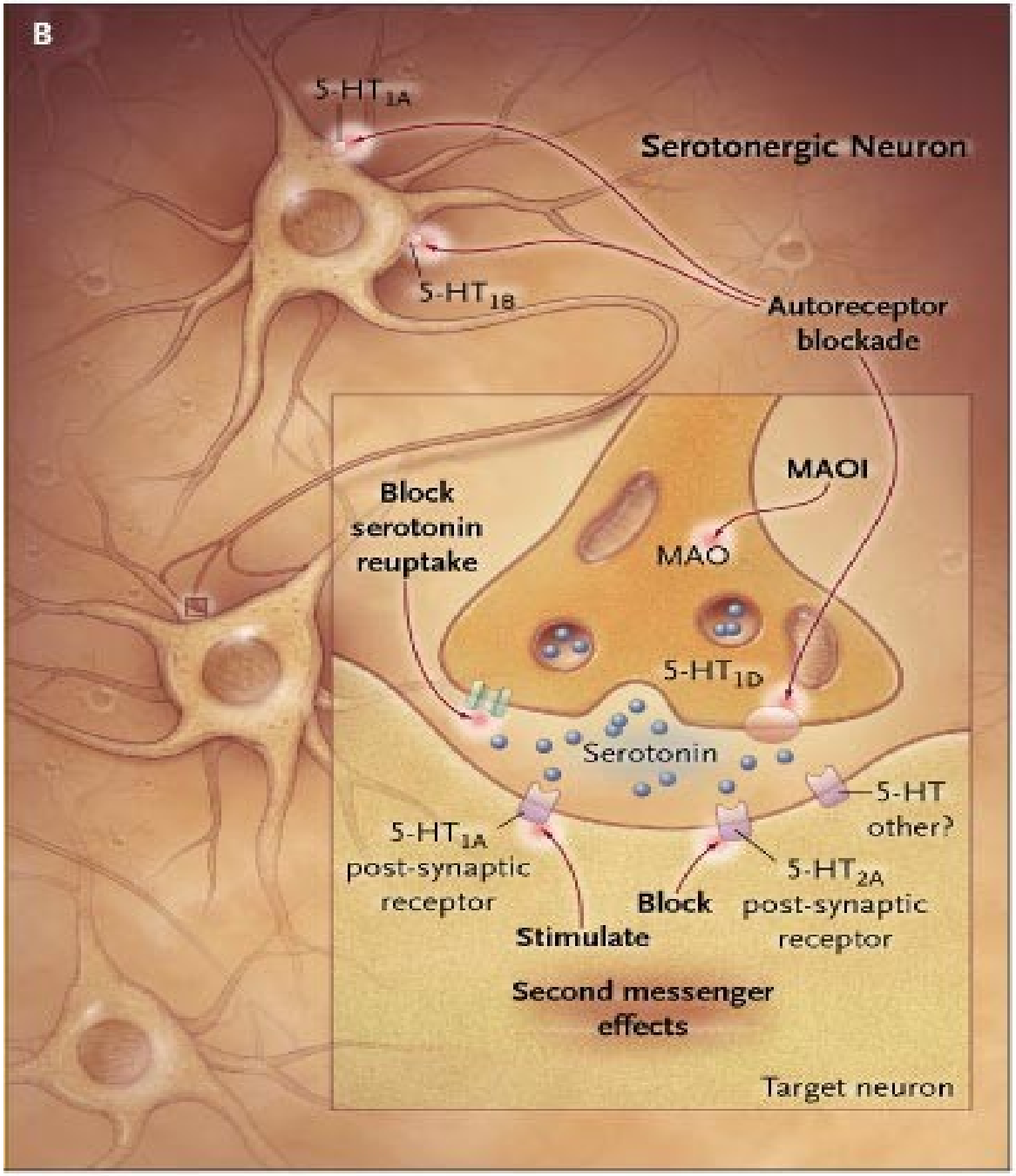


Figure 6.13 Synthesis of histamine and serotonin. (A) Histamine is synthesized from the amino acid histidine. (B) Serotonin is derived from the amino acid tryptophan by a two-step process that requires the enzymes tryptophan-5-hydroxylase and a decarboxylase.


Neurona presináptica
Inhibición de adenil ciclasa
Receptor 5-HT1A
G
AMPc
Liberación de serotonina
Receptor 5-HT2A
Serotonina
Fosfatidilinositol
Neurona postsináptica
Acción biológica

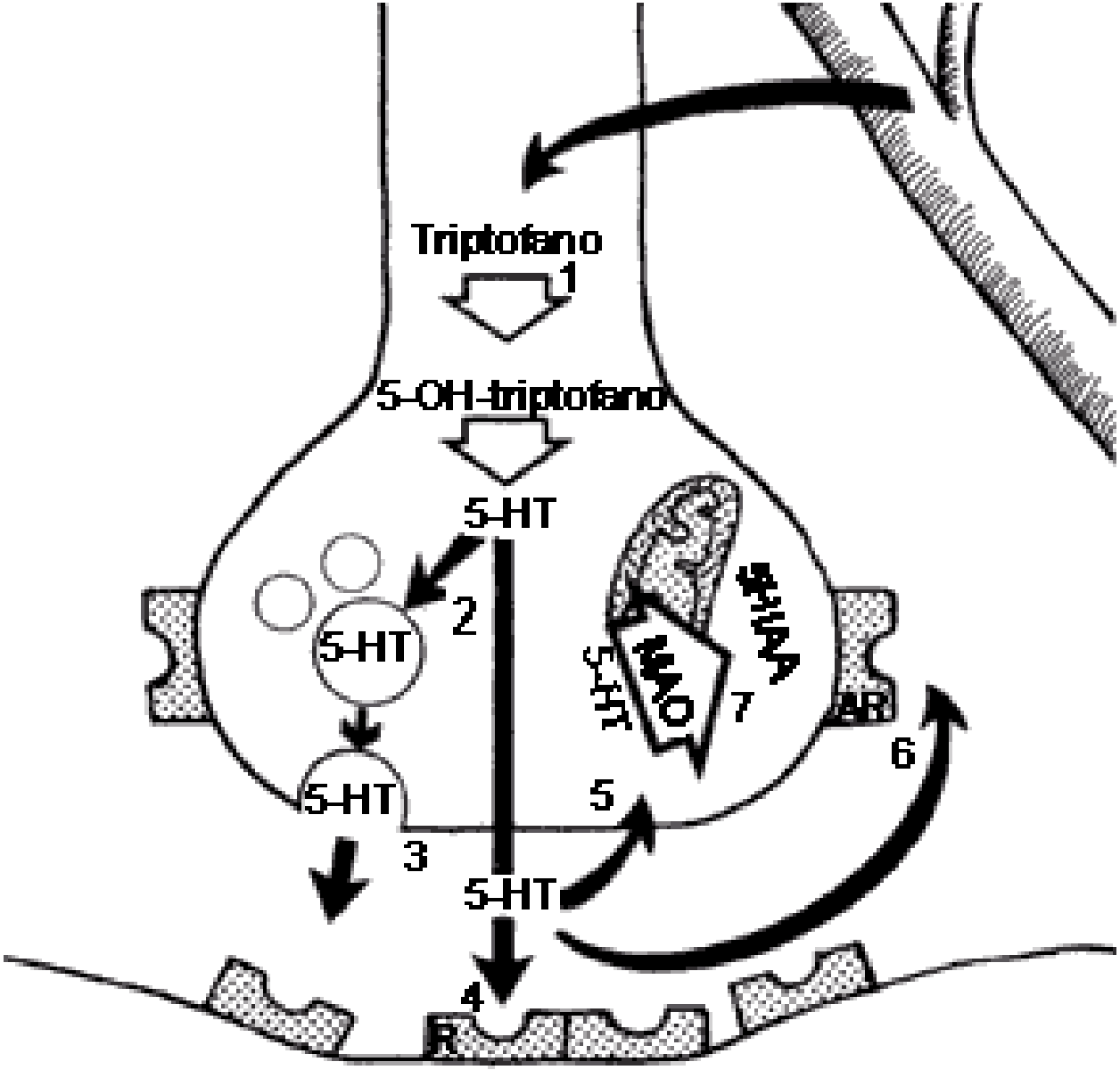

PRESYNAPTIC CELL
"STOP PRODUCTION" SIGNAL
SEROTONIN
AUTORECEPTOR
REUPTAKE TRANSPORTER
SYNAPTIC CLEFT
REGULATORY SIGNAL
SEROTONIN RECEPTOR
POSTSYNAPTIC CELL


B
5-HT1A
Serotonergic Neuron
5-HT1B
Autoreceptor blockade
MAOI
Block serotonin reuptake
MAO
5-HT1D
Serotonin
5-HT other?
5-HT1A post-synaptic receptor
5-HT2A post-synaptic receptor
Block
Stimulate
Second messenger effects
Target neuron

RE

- 5 HT1A:SIST. LIMBICO
- 5-HT1B: SUST. NIGRA, GLOBUS PALIDO
- 5-HT1D: SUST NIGRA, ESTRIADO,SUBTAL. AMIGDAL
- 5-HT1E: GANGLIOS BASALES HIPOCAMPO
- 5-HT1F: HIPOCAMPO INTERPEDUNCULAR Y CEREBELO
- 5-HT2A: PLEXOS COROIDEOS, ESTRIADO HIPOTALAMO
- 5-HT3: TRONCO ENCEFALO AREA POSTREMA SOLIT
- 5-HT4: TURBERCULO OLFATORIO
- 5-HT5: CORTEZA, HIPOCAMPO RNA m
- 5-HT6: ESTRIADO, ACUMBENS
- 5-HT7: TALAMO, HIPOTALAMO E HIPOCAMPO SEPTO Y CORTEZA

5-HT


Triptofano
1
5-OH-triptofano
5-HT
2
5-HT
5-HT
3
5-HT
4
R
5
6
7
AR

Marijuana and the Brain

Medicinal use of the marijuana plant, *Cannabis sativa* (Figure A), dates back thousands of years. Ancient civilizations—including both Greek and Roman societies in Europe, as well as Indian and Chinese cultures in Asia—appreciated that this plant was capable of producing relaxation, euphoria, and a number of other psychopharmacological actions. In more recent times, medicinal use of marijuana has largely subsided (although it remains useful in relieving the symptoms of terminal cancer patients); the recreational use of marijuana (Figure B) has become so popular that some societies have decriminalized its use.

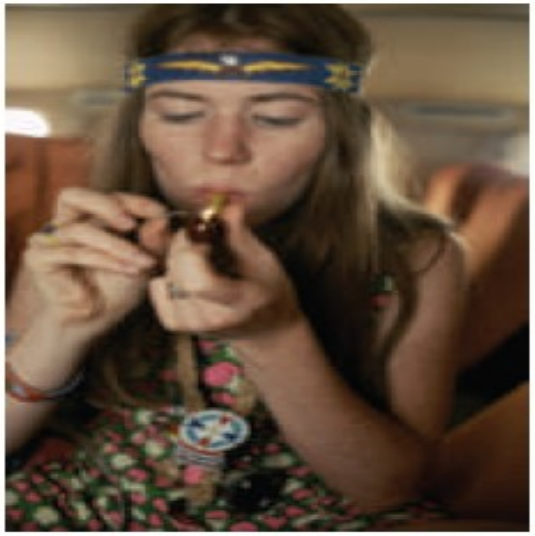
Understanding the brain mechanisms underlying the actions of marijuana was advanced by the discovery that a cannabinoid, Δ^9-tetrahydrocannabinol (THC; Figure C), is the active component of marijuana. This finding led to the development of synthetic derivatives, such as WIN 55,212-2 and rimonabant (see Figure 6.16), that have served as valuable tools for probing the brain actions of THC. Of particular interest is that receptors for these cannabinoids exist in the brain and exhibit marked regional variations in distribution, being especially enriched in the brain areas—such as substantia nigra and caudate putamen—that have been implicated in drug abuse (Figure D). The presence of these brain receptors for cannabinoids led in turn to a search for endogenous cannabinoid compounds in the brain, culminating in the discovery of endocannabinoids such as 2-AG and anandamide (see Figure 6.16). This path of discovery closely parallels the identification of endogenous opioid peptides, which resulted from the search for endogenous morphine-like compounds in the brain (see text and Table 6.2).

Given that THC interacts with brain endocannabinoid receptors, particularly

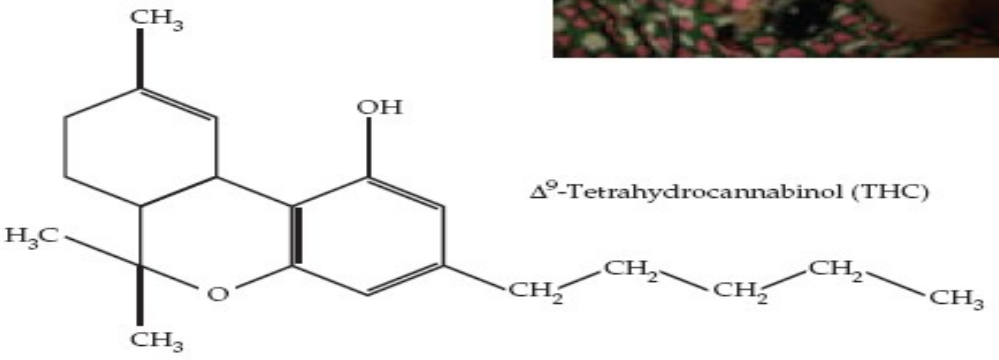
(A)

Cannabis sativa

(B)

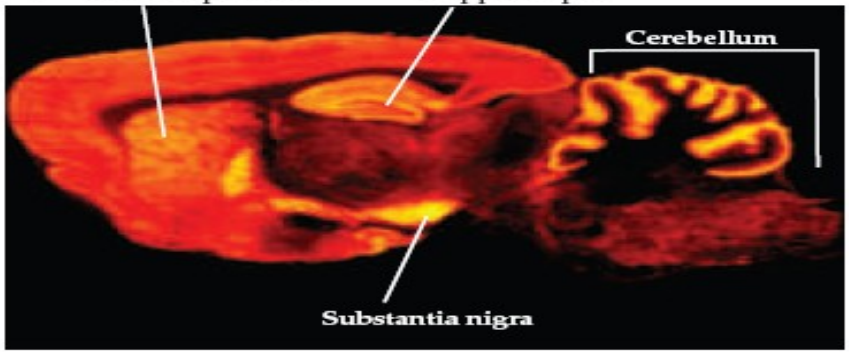
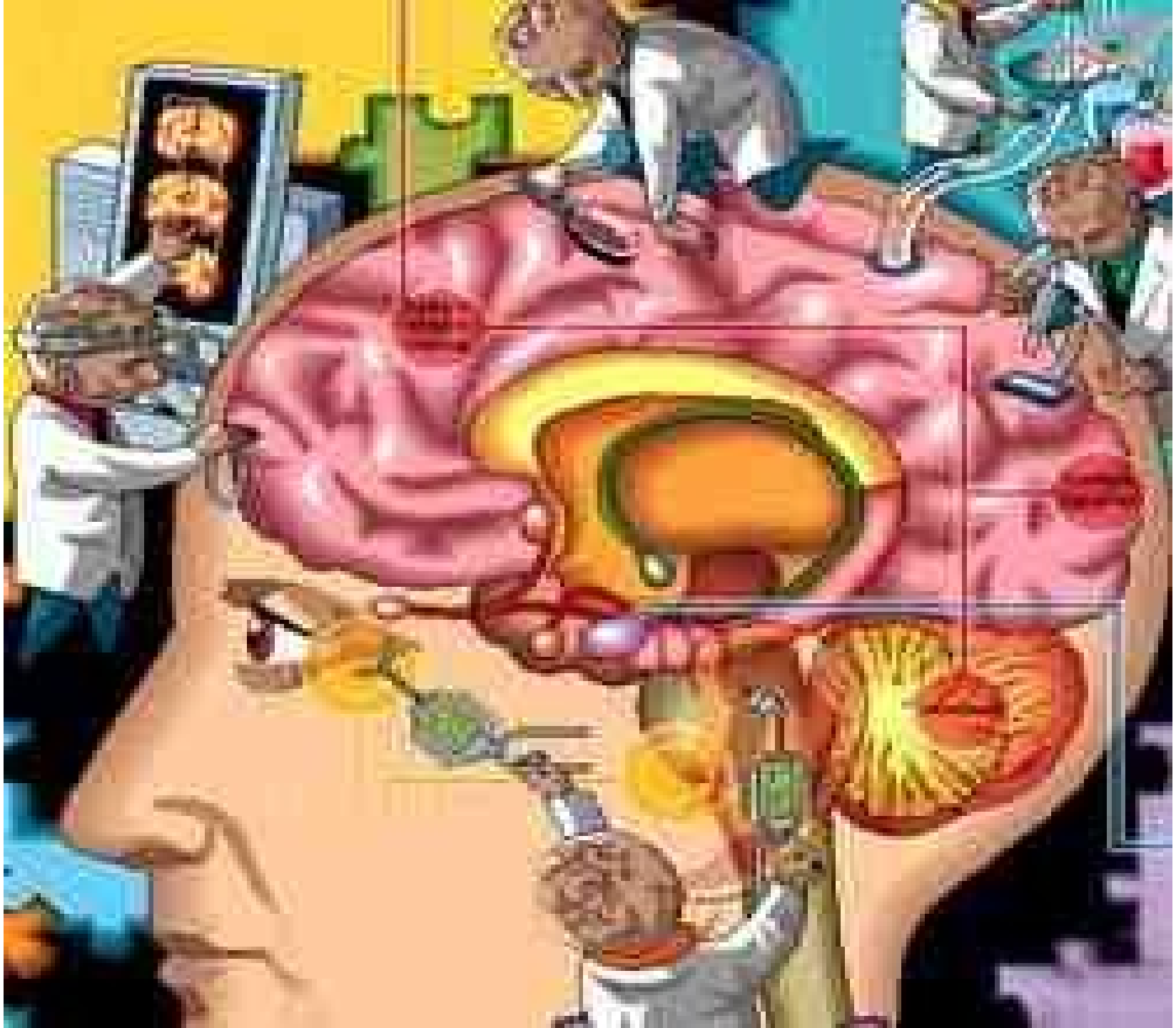


(C)



Δ^9-Tetrahydrocannabinol (THC)

(D)



(A) Leaf of *Cannabis sativa*, the marijuana plant. (B) Smoking ground-up *Cannabis* leaves is a popular method of achieving the euphoric effects of marijuana. (C) Structure of THC (Δ^9-tetrahydrocannabinol), the active ingredient of marijuana. (D) Distribution of brain CB1 receptors, visualized by examining the binding of CP-55,940, a CB1 receptor ligand. (B photo © Henry Diltz/Corbis; C after Iversen, 2003; D courtesy of M. Herkenham, NIMH.)